L Number	Hits	Search Text	DB	Time stamp
1	11557	phenyl and piperidinyl	USPAT; US-PGPUB	2003/02/09 19:48
2	267	(phenyl and piperidinyl) and opioid	USPAT; US-PGPUB	2003/02/09 19:48

EAST

09/755,021

Pregrant version

2002/0132828

09/ 755,021

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TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2	Apr 08	"Ask CAS" for self-help around the clock
NEWS	3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS	4	Apr 09	ZDB will be removed from STN
NEWS	5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS	6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS	7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS	8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS	9	Jun 03	New e-mail delivery for search results now available
NEWS	10	Jun 10	MEDLINE Reload
NEWS	11	Jun 10	PCTFULL has been reloaded
NEWS	12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS	13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS	14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS	15	Jul 30	NETFIRST to be removed from STN
NEWS	16	Aug 08	CANCERLIT reload
NEWS	17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS	18	Aug 08	NTIS has been reloaded and enhanced
NEWS	19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS	20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS	21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS	22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS	23	Sep 03	JAPIO has been reloaded and enhanced
NEWS	24	Sep 16	Experimental properties added to the REGISTRY file
NEWS	25	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS	26	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS	27	Oct 21	EVENTLINE has been reloaded
NEWS	28	Oct 24	BEILSTEIN adds new search fields
NEWS	29	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS	30	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS	31	Nov 18	DKILIT has been renamed APOLLIT
NEWS	32	Nov 25	More calculated properties added to REGISTRY
NEWS	33	Dec 02	TIBKAT will be removed from STN
NEWS	34	Dec 04	CSA files on STN
NEWS	35	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS	36	Dec 17	TOXCENTER enhanced with additional content
NEWS	37	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS	38	Dec 30	ISMEC no longer available
NEWS	39	Jan 13	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS	40	Jan 21	NUTRACEUT offering one free connect hour in February 2003
NEWS	41	Jan 21	PHARMAML offering one free connect hour in February 2003
NEWS	42	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC

NEWS EXPRESS	January 6 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
NEWS HOURS	STN Operating Hours Plus Help Desk Availability

09/ 755,021

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FILE 'HOME' ENTERED AT 17:25:35 ON 09 FEB 2003

=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 17:25:47 ON 09 FEB 2003
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STRUCTURE FILE UPDATES:    7 FEB 2003  HIGHEST RN 487578-67-6
DICTIONARY FILE UPDATES:   7 FEB 2003  HIGHEST RN 487578-67-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1                STR
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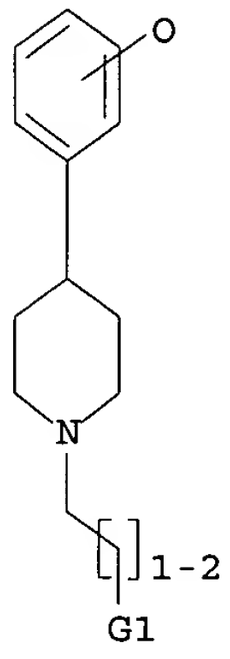
09/ 755,021



G1 O,S,N

Structure attributes must be viewed using STN Express query preparation.

=> s l1 ful
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FULL SCREEN SEARCH COMPLETED - 49832 TO ITERATE

100.0% PROCESSED 49832 ITERATIONS 1309 ANSWERS
SEARCH TIME: 00.00.01

L2 1309 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 148.15 148.36

FILE 'CAPLUS' ENTERED AT 17:26:40 ON 09 FEB 2003

FILE COVERS 1907 - 9 Feb 2003 VOL 138 ISS 7
FILE LAST UPDATED: 7 Feb 2003 (20030207/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l2
L3 173 L2

09/ 755,021

=> file caplus
COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION
FULL ESTIMATED COST | 1.67 | 150.03

FILE 'CAPLUS' ENTERED AT 17:28:51 ON 09 FEB 2003
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 9 Feb 2003 VOL 138 ISS 7
FILE LAST UPDATED: 7 Feb 2003 (20030207/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 173 L2

=> s l4 and (kappa or opioid)
48887 KAPPA
28456 OPIOID
L5 49 L4 AND (KAPPA OR OPIOID)

=> d l5 1- ibib abs fhitstr
YOU HAVE REQUESTED DATA FROM 49 ANSWERS - CONTINUE? Y/(N):y

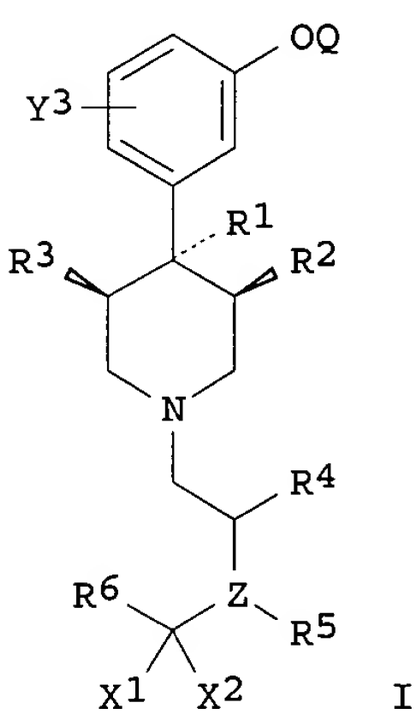
L5 ANSWER 1 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:521701 CAPLUS
DOCUMENT NUMBER: 137:78865
TITLE: Preparation of tetrahydroisoquinolinyl-alkylaminoalkyl-piperidines as selective **kappa** **opioid** receptor ligands
INVENTOR(S): Carroll, F. Ivy; Thomas, James B.; Mascarella, S. Wayne
PATENT ASSIGNEE(S): Research Triangle Institute, USA
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

applicant 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053533	A2	20020711	WO 2002-US482	20020107
WO 2002052533	A3	20020919		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2002132828 A1 20020919 US 2001-755021 20010108
PRIORITY APPLN. INFO.: US 2001-755021 A 20010108
OTHER SOURCE(S): MARPAT 137:78865
GI



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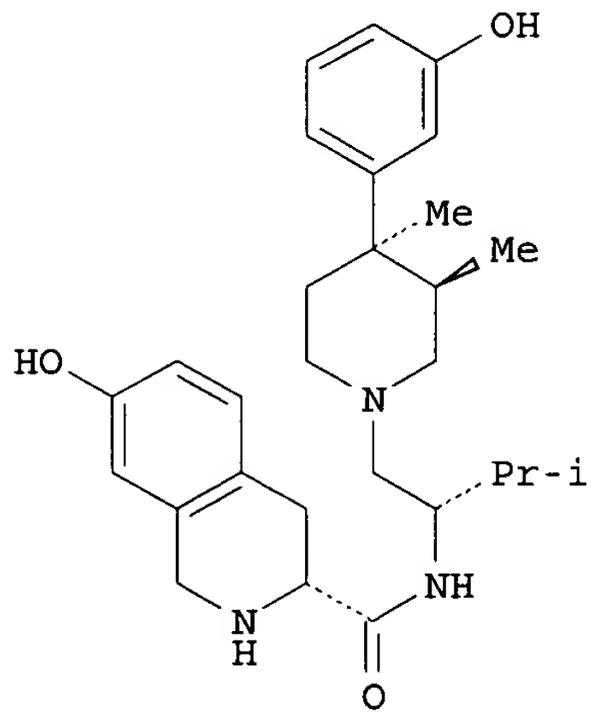


II

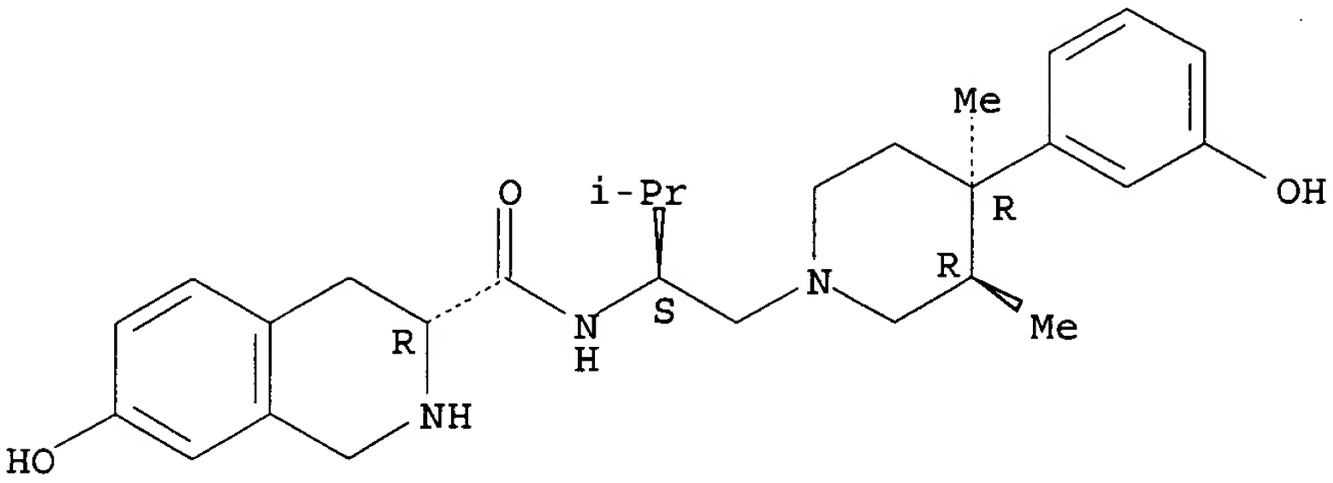
AB Title compds. I [Q = H, CO-alkyl; R1 = alkyl, (alkyl)phenyl, alkyl(heteroaryl), etc.; Y3 = H, OH, Br, Cl, F, CN, CF3, NO2, N3, OR8, CO2R9, etc.; R2 = H, alk(en/yn)yl, CH2-aryl; R3 = H, alk(en/yn)yl, CH2-aryl wherein R2-3 may be bonded together to form a alkyl group; R4 = H, alkyl, carboxy, etc; Z = N, O, S, where Z = O, S, there is no R5; R5 = H, alk(en/yn)yl, CH2-carboxy, etc.; R6 = tetrahydroisoquinolinyl, indazolyl, etc.; X1 = H, alk(en/yn)yl; X2 = H, alk(en/yn)yl or X1-2 together form =O, =S, =NH; R7 = H, alkyl, CH2-aryl; R8 = H, alkyl, CH2-aryl] were prepd. For instance, (+)-(3R,4R)-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidine was coupled to Boc-L-valine (THF, BOP, Et3N), the resulting adduct deprotected (CH2Cl2, TFA) and the amide reduced (BH3.bul.SMe2). The resulting intermediate was coupled to (3R)-2-(tert-butoxycarbonyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (THF, BOP, Et3N) and deprotected as above to give II. In an assay using human cloned **opioid** receptors, II had Ki = 0.006 nM for the .**kappa**.-receptor (compared to nor-BNI Ki = 0.07 nM) and was selective for the **kappa** receptor with Ki .mu./. **kappa**. = 570 and Ki .delta./.**kappa**. = 16,667. I are useful for the treatment of cocaine or heroine addiction.

IT **361444-66-8P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug, reactant; prepn. of tetrahydroisoquinolinyl-alkylaminoalkyl-piperidines as selective **kappa opioid** receptor ligands)

RN 361444-66-8 CAPLUS

CN 3-Isoquinolinecarboxamide, 1,2,3,4-tetrahydro-7-hydroxy-N-[(1S)-1-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl]-, (3R)- (9CI) (CA INDEX NAME)

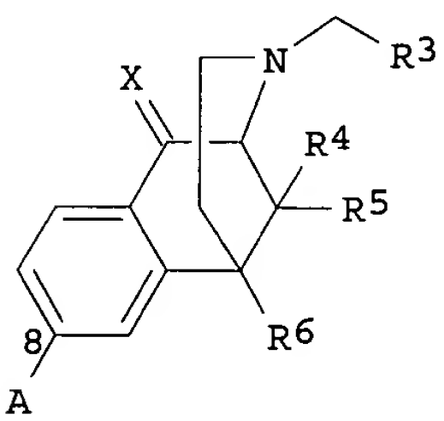
Absolute stereochemistry.



L5 ANSWER 2 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:353436 CAPLUS
DOCUMENT NUMBER: 136:369883
TITLE: Preparation of 8-substituted-2,6-methano-3-benzazocines for therapeutic use as **opioid** receptor agnonists
INVENTOR(S): Wentland, Mark P.
PATENT ASSIGNEE(S): Rensselaer Polytechnic Institute, USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002036573	A2	20020510	WO 2001-US45581	20011031
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002027135	A5	20020515	AU 2002-27135	20011031

PRIORITY APPLN. INFO.: US 2000-244438P P 20001031
WO 2001-US45581 W 20011031
OTHER SOURCE(S): CASREACT 136:369883; MARPAT 136:369883
GI



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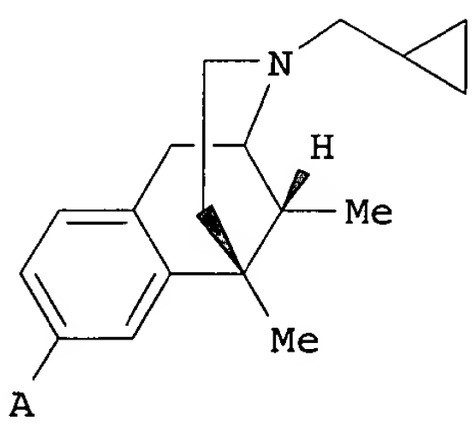


II

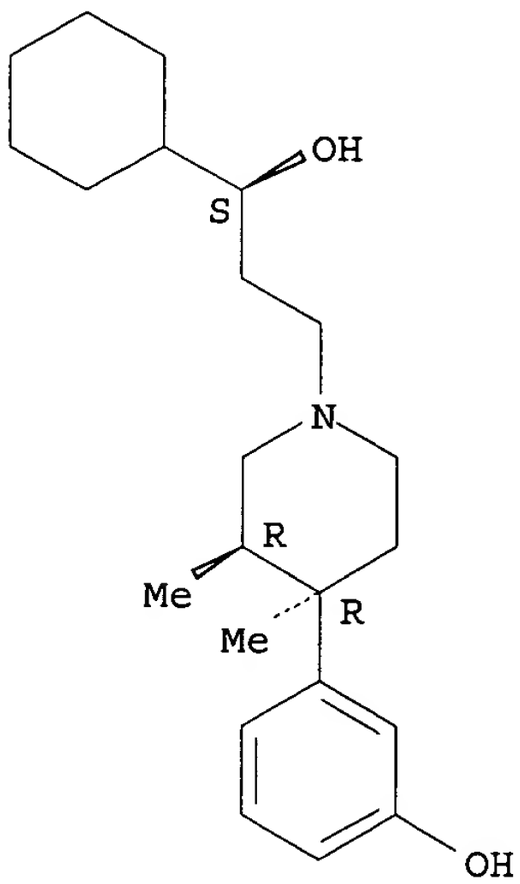
AB 8-Substituted-2,6-methano-3-benzazocines, such as I [R3 = H, alkyl,

alkenyl, aryl, heterocyclyl, cycloalkyl, etc.; R4 = H, OH, NH2, alkoxy, hydroxyalkyl, etc.; R5, R6 = alkyl; A = CH2OH, CH2SH, CH2NH2, carboxy, carboxamido, thiocarboxamido, etc.; X = H2, O], were prepd. for pharmaceutical use as analgesics, anti-diarrheal agents, anticonvulsants, antitussives and anti-addiction medications. Thus, benzazocine II (A = CN) was prepd. in 80% yield by reaction of triflate II (A = OSO2CF3) and Zn(CN)2 in DMF using Pd(PPh3)4. The prepd. benzazocines were tested for **opioid** receptor binding activity in mice, e.g. with II (A = CONH2) giving Ki values of 0.41 .+-. 0.07, 8.3 .+-. 0.49 and 0.53 .+-. 0.06 nM for the .mu., .delta. and .**kappa**. **opioid** receptors, resp. The 8-carboxamides, thiocarboxamides, hydroxyamidines and formamides were preferred.

IT **119193-09-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 8-substituted-2,6-methano-3-benzazocines for therapeutic use as **opioid** receptor agnonists)

RN 119193-09-8 CAPLUS
CN 1-Piperidinepropanol, .alpha.-cyclohexyl-4-(3-hydroxyphenyl)-3,4-dimethyl-, (.alpha.S,3R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 3 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:31619 CAPLUS
DOCUMENT NUMBER: 136:96697
TITLE: Human melanin concentrating hormone receptor MCH1, its DNA, its synthetic ligands and diagnostic and therapeutic uses thereof
INVENTOR(S): Salon, John A.; Laz, Thomas M.; Nagorny, Raisa; Wilson, Amy E.
PATENT ASSIGNEE(S): Synaptic Pharmaceutical Corporation, USA
SOURCE: PCT Int. Appl., 524 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

09/ 755,021

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002002744	A2	20020110	WO 2001-US21350	20010705
WO 2002002744	A3	20020808		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1246847	A2	20021009	EP 2001-952456	20010705

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:	US 2000-610635	A	20000705
	WO 2001-US21350	W	20010705

AB This invention provides an isolated nucleic acid encoding a human MCH1 receptor, a purified human MCH1 receptor, vectors comprising isolated nucleic acid encoding a human MCH1 receptor, cells comprising such vectors, antibodies directed to a human MCH1 receptor, nucleic acid probes useful for detecting nucleic acid encoding human MCH1 receptors, antisense oligonucleotides complementary to unique sequence of nucleic acid encoding human MCH1 receptors, transgenic, nonhuman animals which express DNA encoding a normal or mutant human MCH1 receptor, methods of isolating a human MCH1 receptor, methods of treating an abnormality that is linked to the activity of a human MCH1 receptor, as well as methods of detg. binding of compds. to mammalian MCH1 receptors. This invention provides a method of modifying the feeding behavior of a subject which comprises administering to the subject an amt. of an MCH1 antagonist effective to decrease the body mass of the subject and/or decrease the consumption of food by the subject. This invention further provides a method of treating a subject suffering from depression and/or anxiety which comprises administering to the subject an amt. of an MCH1 antagonist effective to treat the subject's depression and/or anxiety.

IT **387825-77-6P**

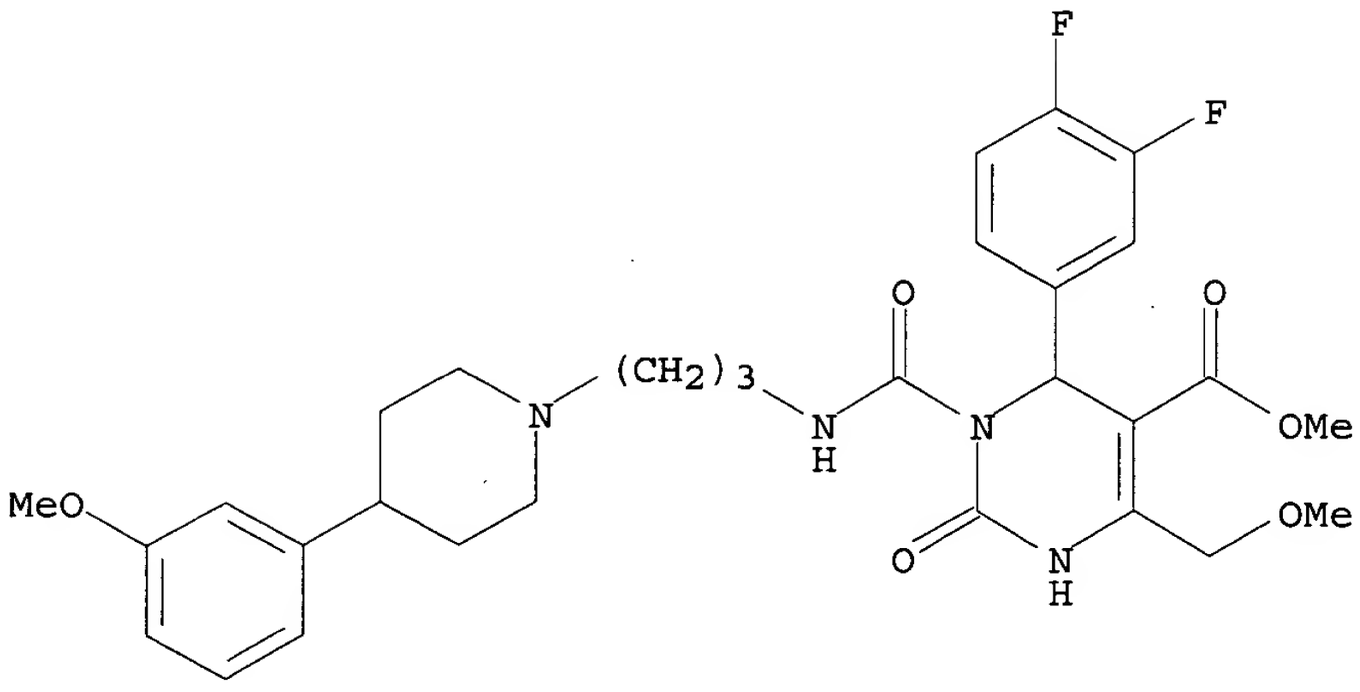
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(human melanin concg. hormone receptor MCH1, its DNA, its synthetic ligands and diagnostic and therapeutic uses thereof)

RN 387825-77-6 CAPLUS

CN 5-Pyrimidinecarboxylic acid, 6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-4-(methoxymethyl)-1-[[[3-[4-(3-methoxyphenyl)-1-piperidinyl]propyl]amino]carbonyl]-2-oxo-, methyl ester, monohydrochloride, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



● HCl

L5 ANSWER 4 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:2292 CAPLUS
DOCUMENT NUMBER: 137:134182
TITLE: Alvimopan (ADL 8-2698) Is a Novel Peripheral **Opioid** Antagonist
AUTHOR(S): Schmidt, William K.
CORPORATE SOURCE: Adolor Corporation, Exton, PA, 19341-1127, USA
SOURCE: American Journal of Surgery (2001), 182(5A), 27S-38S
CODEN: AJSUAB; ISSN: 0002-9610
PUBLISHER: Excerpta Medica, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Alvimopan (ADL 8-2698; Adolor Corporation, Exton, PA, USA) is a novel, peripherally restricted **opioid** antagonist. After oral administration, it has activity specific to the gastrointestinal (GI) tract. ADL 8-2698 has low systemic absorption and a high affinity for .mu.-**opioid** receptors. In healthy subjects, ADL 8-2698 antagonized loperamide-induced changes in GI transit and prevented morphine-induced delays in oral-cecal transit time without antagonizing centrally mediated **opioid** effects, such as analgesia or pupillary constriction. In the treatment of **opioid** naive patients who underwent surgery and received opioids for acute pain, oral ADL 8-2698 (6.0 mg) improved the management of postoperative ileus (POI) by shortening the time to achieve normal bowel function and, ultimately, hospital stay. Postoperative nausea and vomiting and the overall incidence of all GI side effects were reduced in patients treated with ADL 8-2698 for POI. Analgesia was not compromised, because there were no changes in median **opioid** consumption or Visual Analog Scale (VAS) pain scores in patients treated with ADL 8-2698 vs. patients treated with placebo. No drug-related side effects were obsd. in acute pain postsurgical patients in the initial POI study. In patients treated with opioids for chronic pain or **opioid** addiction, lower doses of oral ADL 8-2698 (0.5 to 3.0 mg) reversed **opioid** bowel dysfunction (OBD) and normalized GI activity. These effects were evident without compromising **opioid** analgesia or inducing central nervous system symptoms of withdrawal. Some chronic **opioid** patients receiving apparently supramaximal doses of ADL 8-2698 (.gtoreq.3.0 mg) reported localized GI side effects, possibly indicative of a localized GI withdrawal response. The most common side effects of

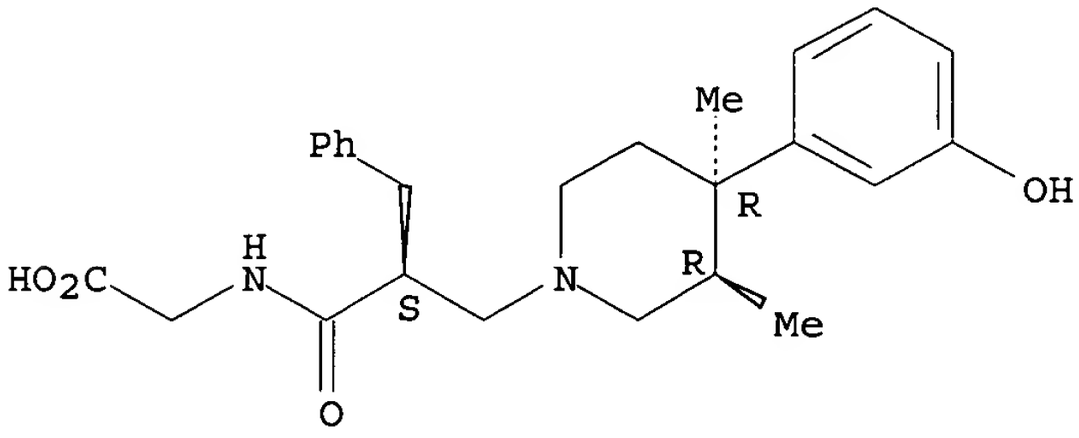
ADL 8-2698 in chronic pain patients with OBD were abdominal pain, flatulence, and diarrhea. These effects were not obsd. in most OBD patients receiving lower doses of ADL 8-2698. Overall, ADL 8-2698 was well tolerated in clin. trials. Further studies to evaluate the efficacy and safety of ADL 8-2698 in clin. practice are in progress.

IT **156053-89-3**, Alvimopan
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alvimopan is novel peripheral **opioid** antagonist used in treatment of **opioid** related gastrointestinal side effects)

RN 156053-89-3 CAPLUS

CN Glycine, N-[(2S)-2-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 49 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:869020 CAPLUS

DOCUMENT NUMBER: 136:677

TITLE: Novel methods and compositions involving opioids and antagonists thereof

INVENTOR(S): Farrar, John J.

PATENT ASSIGNEE(S): Farrar, John, USA

SOURCE: U.S. Pat. Appl. Publ., 39 pp., Cont.-in-part of U.S. Ser. No. 304,199, abandoned.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001047005	A1	20011129	US 2000-725661	20001129
US 6451806	B2	20020917		

PRIORITY APPLN. INFO.: US 2000-304199 B2 20000427

OTHER SOURCE(S): MARPAT 136:677

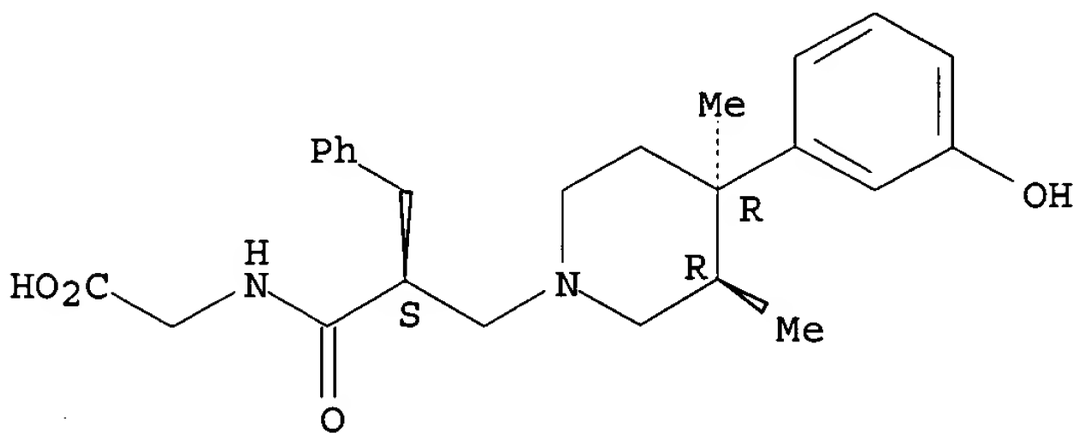
AB Novel methods and compns. comprising opioids and **opioid** antagonists. In preferred embodiments, the methods and compns. comprise opioids and peripheral mu **opioid** antagonist compds. The methods and compns. are particularly suitable for treating and/or preventing side effects assocd. with opioids including, for example, constipation, vomiting and/or nausea.

IT **156053-89-3**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention and treatment of **opioid** side effects with .mu.-**opioid** antagonists)

09/ 755,021

RN 156053-89-3 CAPLUS
CN Glycine, N-[(2S)-2-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L5 ANSWER 6 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:798759 CAPLUS
DOCUMENT NUMBER: 135:339259
TITLE: Methods using .mu. **opioid** antagonist compounds for the treatment and prevention of ileus
INVENTOR(S): Farrar, John J.; Schied, Peter J.; Schmidt, William K.; Carpenter, Randall L.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 24 pp., Cont.-in-part of U.S. Provisional Ser. No. 287,560, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001036951	A1	20011101	US 2000-725708	20001129
US 6469030	B2	20021022		
US 2002188005	A1	20021212	US 2002-171299	20020613

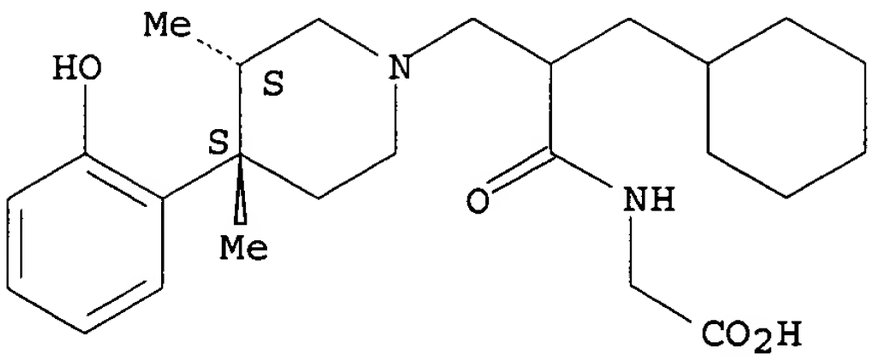
PRIORITY APPLN. INFO.: US 2000-287560P P 20000427
US 2000-725708 A3 20001129
OTHER SOURCE(S): MARPAT 135:339259

AB Methods are disclosed for the treatment and/or prevention of ileus. The methods may comprise administering to a patient an effective amt. of a peripheral .mu. **opioid** antagonist compd. Preferred compds. for use in the methods include piperidine-N-alkylcarboxylates, quaternary morphinans, opium alkaloid derivs. and quaternary benzomorphans. The methods are particularly suitable for treating and/or preventing postsurgical ileus and postpartum ileus.

IT **371154-35-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.mu. **opioid** antagonist compds. for treatment and prevention of ileus)

RN 371154-35-7 CAPLUS
CN Glycine, N-[3-cyclohexyl-2-[[(3R,4R)-4-(2-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



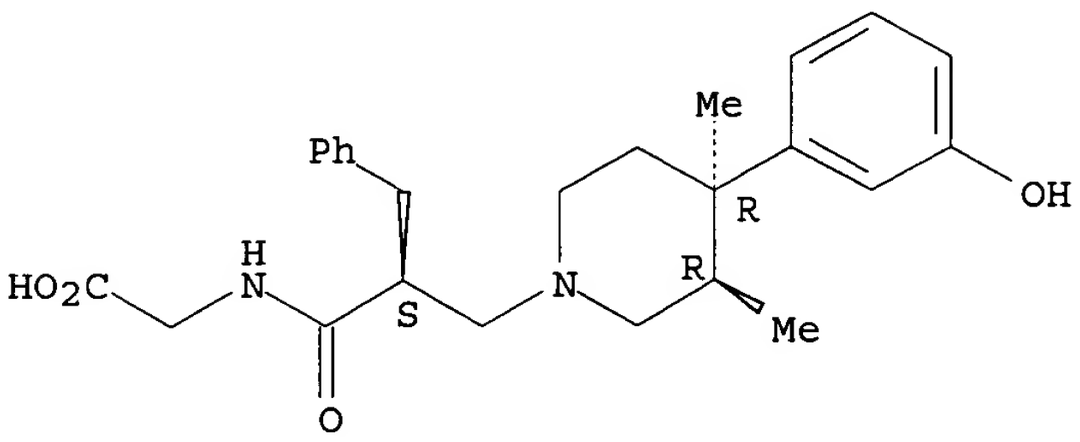
L5 ANSWER 7 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:733273 CAPLUS
DOCUMENT NUMBER: 136:63982
TITLE: Selective postoperative inhibition of gastrointestinal **opioid** receptors
AUTHOR(S): Taguchi, Akiko; Sharma, Neeru; Saleem, Rao M.; Sessler, Daniel I.; Carpenter, Randall L.; Seyedsadr, Mahmoud; Kurz, Andrea
CORPORATE SOURCE: Dep. Anesthesiology, Washington Univ., St. Louis, MO, 63110, USA
SOURCE: New England Journal of Medicine (2001), 345(13), 935-940
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Postoperative recovery of gastrointestinal function and resumption of oral intake are crit. determinants of the length of hospital stay. Although opioids are effective treatments for postoperative pain, they contribute to the delayed recovery of gastrointestinal function. We studied the effects of ADL 8-2698, an investigational **opioid** antagonist with limited oral absorption that does not readily cross the blood-brain barrier, on postoperative gastrointestinal function and the length of hospitalization. We randomly assigned 79 patients - including 1 whose surgery was canceled - to receive one capsule contg. 1 mg or 6 mg of ADL 8-2698 or an identical-appearing placebo capsule two hours before major abdominal surgery and then twice daily until the first bowel movement or until discharge from the hospital. Data were analyzed for 26 patients in each of the three groups; all received opioids for postoperative pain relief. Observers who were unaware of the group assignments evaluated the outcomes. Fifteen patients underwent partial colectomy and 63 underwent total abdominal hysterectomy. Patients given 6 mg of ADL 8-2698 had significantly faster recovery of gastrointestinal function than those given placebo. The median time to the first passage of flatus decreased from 70 to 49 h (P = 0.03), the median time to the first bowel movement decreased from 111 to 70 h (P = 0.01), and the median time until patients were ready for discharge decreased from 91 to 68 h (P = 0.03). Effects in the group that received 1 mg of ADL 8-2698 were less pronounced. Selective inhibition of gastrointestinal **opioid** receptors by an antagonist with limited oral absorption that does not readily cross the blood-brain barrier speeds recovery of bowel function and shortens the duration of hospitalization.

IT **156053-89-3**, ADL 8-2698
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective postoperative inhibition of gastrointestinal **opioid** receptors)

RN 156053-89-3 CAPLUS
CN Glycine, N-[(2S)-2-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]- (9CI) (CA INDEX NAME)

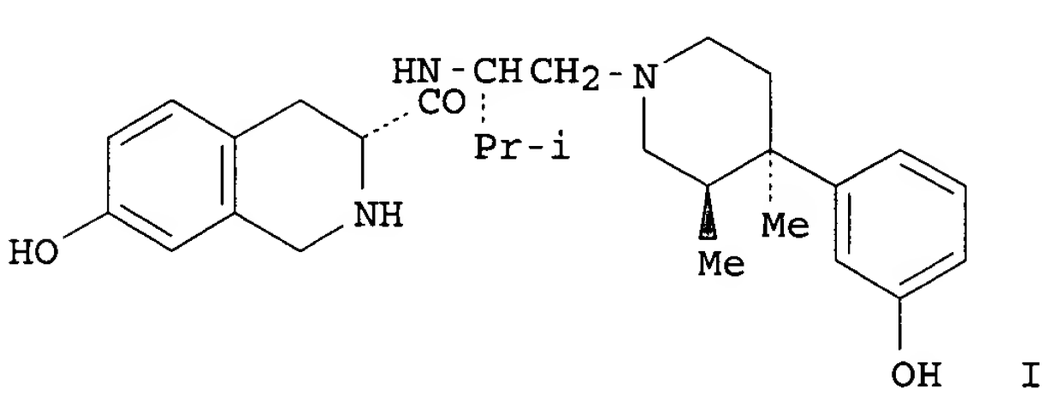
Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 49 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:510739 CAPLUS
DOCUMENT NUMBER: 135:251896
TITLE: Identification of the first trans-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine derivative to possess highly potent and selective **opioid** . **kappa**. receptor antagonist activity
AUTHOR(S): Thomas, James B.; Atkinson, Robert N.; Rothman, Richard B.; Fix, Scott E.; Mascarella, S. Wayne; Vinson, N. Ariane; Xu, Heng; Dersch, Christina M.; Lu, Y. -F.; Cantrell, Buddy E.; Zimmerman, Dennis M.; Carroll, F. Ivy
CORPORATE SOURCE: Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, NC, 27709, USA
SOURCE: Journal of Medicinal Chemistry (2001), 44(17), 2687-2690
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

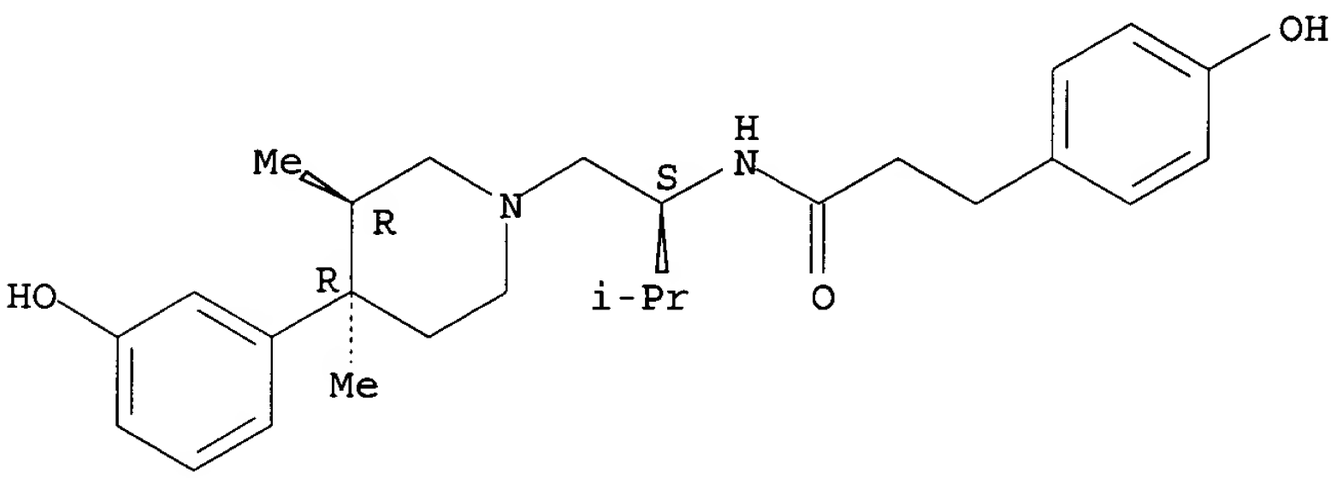
AB A structurally novel **opioid** .**kappa**. receptor selective ligand has been identified. This compd., (3R)-7-hydroxy-N-((1S)-1-{[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl}-2-methylpropyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide (JDTic, I) demonstrated high affinity for the .**kappa**. receptor in the binding assay (.**kappa**. Ki = 0.3 nM) and highly potent and selective .**kappa**. antagonism in the [35S]GTP-.gamma.-S assay using cloned **opioid** receptors (.**kappa**. Ki = 0.006 nM, .mu./.**kappa**. ratio = 570, .delta./.**kappa**. ratio > 16600).

IT **220124-25-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(identification of trans-(3R,4R)- dimethyl-4-(3-hydroxyphenyl)piperidine deriv. as highly potent and selective **opioid .kappa.** receptor antagonist)

RN 220124-25-4 CAPLUS
CN Benzenepropanamide, 4-hydroxy-N-[(1S)-1-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:435040 CAPLUS
DOCUMENT NUMBER: 135:29144
TITLE: Methods using a peripheral .mu. **opioid** antagonist for the treatment and prevention of ileus
INVENTOR(S): Farrar, John J.; Schied, Peter J.; Schmidt, William K.; Carpenter, Randall L.
PATENT ASSIGNEE(S): Adolor Corporation, USA
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001042207	A2	20010614	WO 2000-US42313	20001129
WO 2001042207	A3	20020502		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001039705	A5	20010618	AU 2001-39705	20001129
EP 1244448	A2	20021002	EP 2000-992255	20001129
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 1999-450920 A 19991129
WO 2000-US42313 W 20001129

OTHER SOURCE(S): MARPAT 135:29144

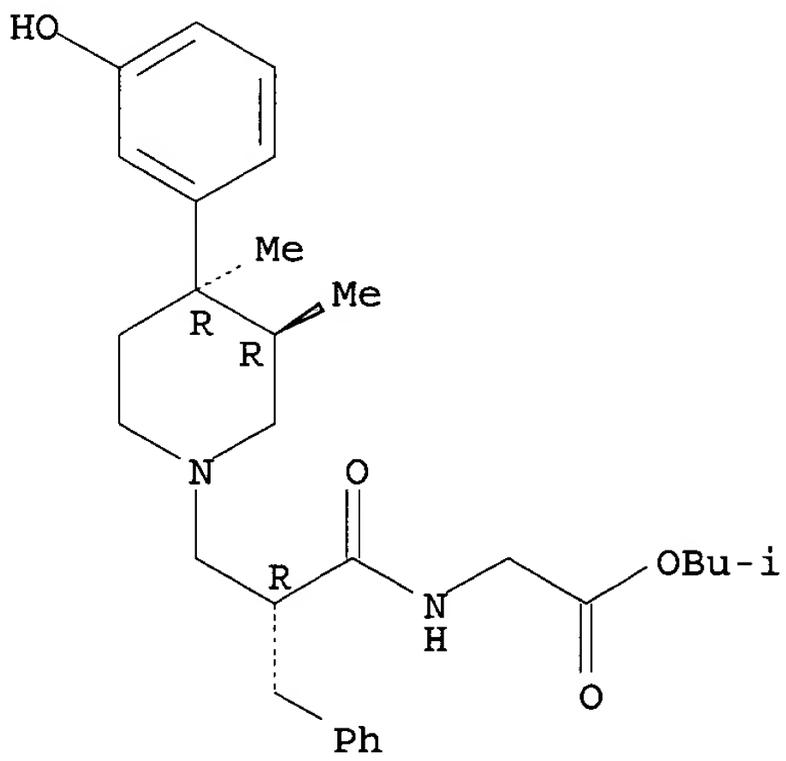
AB Methods are provided for the treatment and/or prevention of ileus. The methods may comprise administering to a patient an effective amt. of a

peripheral .mu. **opioid** antagonist compd. Preferred compds. for use in the methods include piperidine-N-alkylcarboxylates, quaternary morphinans, opium alkaloid derivs. and quaternary benzomorphans. The methods are particularly suitable for treating and/or preventing postsurgical ileus and postpartum ileus.

IT **145590-95-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peripheral .mu. **opioid** antagonist for treatment and prevention of ileus)

RN 145590-95-0 CAPLUS
CN Glycine, N-[(2R)-2-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-, 2-methylpropyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 10 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:434812 CAPLUS
DOCUMENT NUMBER: 135:29160
TITLE: Methods using peripheral .mu. **opioid** antagonists for the treatment and prevention of dizziness and pruritus
INVENTOR(S): Carpenter, Randall L.
PATENT ASSIGNEE(S): Adolor Corporation, USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001041705	A2	20010614	WO 2000-US42310	20001129
WO 2001041705	A3	20011220		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2001041369 A5 20010618 AU 2001-41369 20001129

PRIORITY APPLN. INFO.: US 1999-450812 A 19991129

WO 2000-US42310 W 20001129

OTHER SOURCE(S): MARPAT 135:29160

AB Methods are provided for the treatment and/or prevention of dizziness and/or pruritus. The methods may comprise administering to a patient an effective amt. of a peripheral .mu. **opioid** antagonist compd. Preferred compds. for use in the methods include piperidine-N-alkylcarboxylates, quaternary morphinans, opium alkaloid derivs. and quaternary benzomorphans. The methods are particularly suitable for treating and/or preventing dizziness and/or pruritus assocd. with **opioid** compds.

IT **145590-95-0**

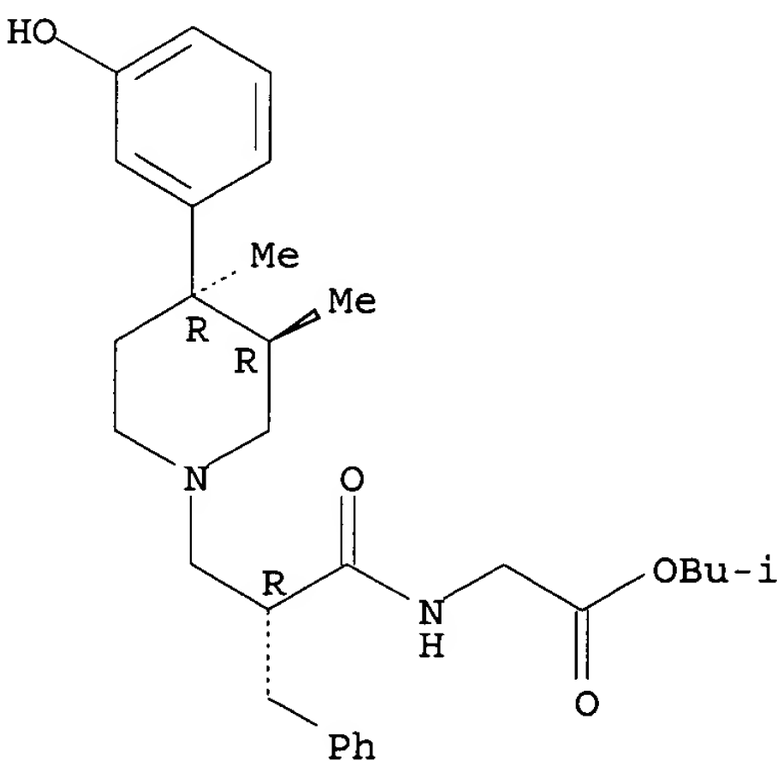
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(peripheral .mu. **opioid** antagonist for treatment and prevention of dizziness and pruritus)

RN 145590-95-0 CAPLUS

CN Glycine, N-[(2R)-2-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-, 2-methylpropyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 11 OF 49 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:396624 CAPLUS

DOCUMENT NUMBER: 135:14336

TITLE: Compositions containing opioids and their antagonists

INVENTOR(S): Farrar, John J.

PATENT ASSIGNEE(S): Adolor Corporation, USA

SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001037785 A2 20010531 WO 2000-US42315 20001129
WO 2001037785 A3 20020110
WO 2001037785 C2 20020829
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 2001039706 A5 20010604 AU 2001-39706 20001129
EP 1244447 A2 20021002 EP 2000-992256 20001129
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: US 1999-450806 A 19991129
WO 2000-US42315 W 20001129
OTHER SOURCE(S): MARPAT 135:14336

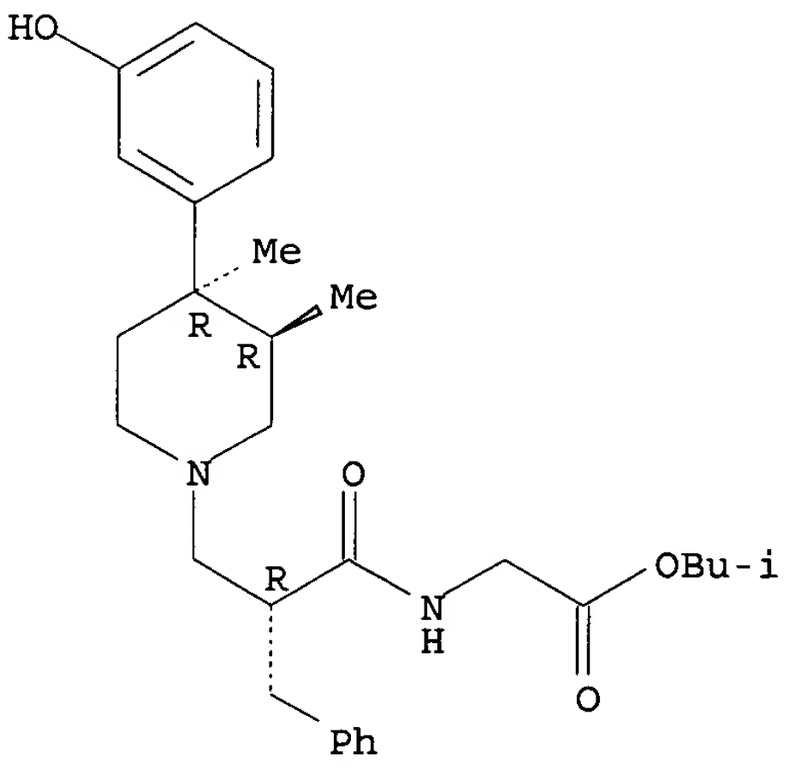
AB Methods and compns. comprise opioids and **opioid** antagonists, e.g., peripheral .mu.-**opioid** antagonists. Methods and compns. are particularly suitable for treating and/or preventing side effects (assocd. with opioids) such as e.g., constipation, vomiting and/or nausea.

IT **145590-95-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. contg. opioids and their antagonists)

RN 145590-95-0 CAPLUS

CN Glycine, N-[(2R)-2-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-, 2-methylpropyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 12 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:102913 CAPLUS
DOCUMENT NUMBER: 135:117075
TITLE: ADL 8-2698, a trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine, prevents gastrointestinal effects of intravenous morphine without affecting analgesia
AUTHOR(S): Liu, Spencer S.; Hodgson, Peter S.; Carpenter, Randall L.; Fricke, James R., Jr.

09/ 755,021

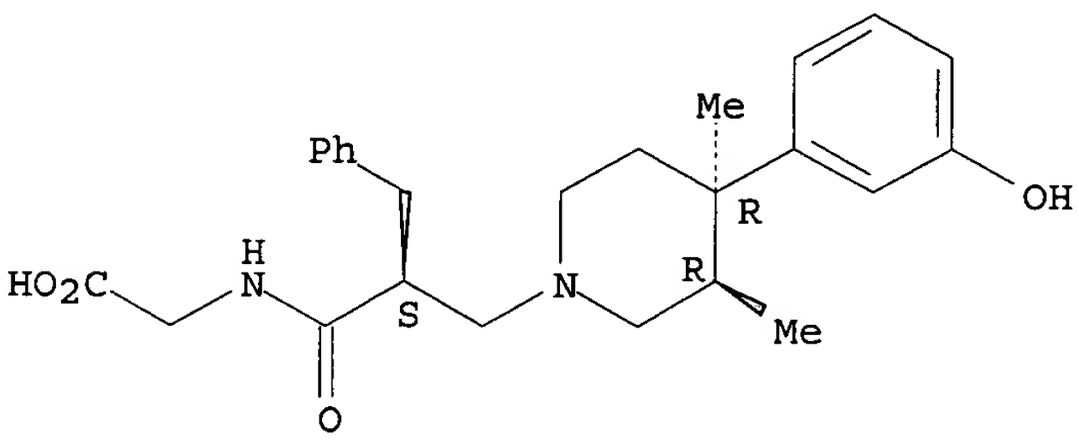
CORPORATE SOURCE: Departments of Anesthesiology, Virginia Mason Medical Center, The University of Washington, Seattle, WA, USA
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis, MO, United States) (2001), 69(1), 66-71
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB ADL-8-2698 is a novel peripherally restricted **opioid** antagonist that may selectively prevent **opioid**-induced gastrointestinal effects without reversing analgesia. Gastrointestinal transit time (lactulose hydrogen breath test) was measured in 14 volunteers with oral and i.v. placebo, oral placebo and i.v. morphine (0.05 mg .cntdot. kg-1), and oral ADL 8-2698 (4 mg) and i.v. morphine (0.05 mg .cntdot. kg-1) in a double blind, cross-over study. Morphine prolonged gastrointestinal transit time from 69 to 103 min (P =.005); this was prevented by ADL 8-2698 (P =.004). Postoperatively, 45 patients were randomly assigned in a double-blind fashion to receive ADL 8-2698 (4 mg) or placebo and i.v. morphine (0.15 mg/kg) or to receive oral and i.v. placebo. Analgesia and pupil constriction were measured. Morphine analgesia and pupil constriction were unaffected by ADL 8-2698 and differed from placebo (P <.002). We conclude that ADL 8-2698 prevents morphine-induced increases in gastrointestinal transit time by means of selective peripheral **opioid** antagonism without affecting central **opioid** analgesia.

IT **156053-89-3**, ADL 8-2698
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ADL 8-2698 trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine prevents gastrointestinal effects of i.v. morphine without affecting analgesia)

RN 156053-89-3 CAPLUS
CN Glycine, N-[(2S)-2-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:739097 CAPLUS
DOCUMENT NUMBER: 134:13083
TITLE: Three-dimensional quantitative structure-activity relationship of **opioid** antagonists with potent anorexic activity of 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine
AUTHOR(S): Li, Hua; Xu, Lu; Su, Qiang
CORPORATE SOURCE: Department of Chemistry, Northwest University, Xian, 710069, Peop. Rep. China
SOURCE: Gaodeng Xuexiao Huaxue Xuebao (2000), 21(10),

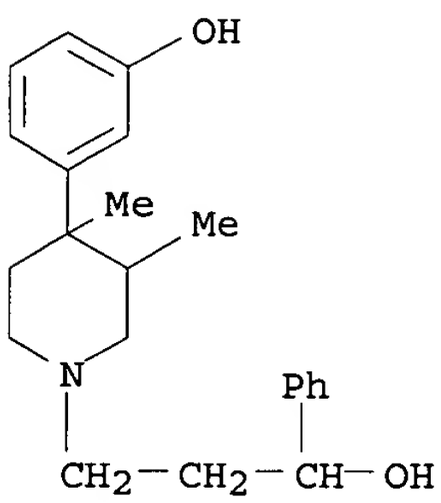
09/ 755,021

1479-1483
CODEN: KTHPDM; ISSN: 0251-0790
PUBLISHER: Gaodeng Jiaoyu Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB A series of 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine **opioid** antagonists with varying substituents on the nitrogen were evaluated for their effect on food consumption in obese Zucker rats. In developing three-dimensional quant. structure-activity relationship(3D-QSAR) studies for this series of **opioid** antagonists, different structure alignments have been tested to predict the anorexic activities. The interaction energies between mols. and the probe atom were then correlated with anorexic activity using partial least squares (PLS) method. The steric and electrostatic features of the 3D-QSAR were presented in the form of std. deviation coeff. contour maps of steric and electrostatic fields. The results showed that 3D-QSAR results are much better than the results obtained by 2D-QSAR.

IT **82970-70-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(three-dimensional quant. structure-activity relationship of **opioid** antagonists with potent anorexic activity of 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine)

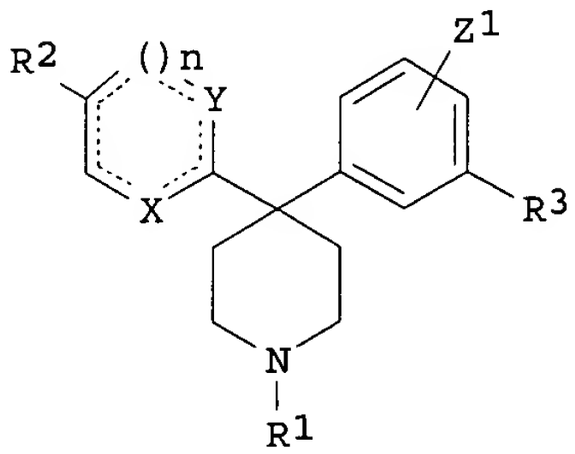
RN 82970-70-5 CAPLUS
CN 1-Piperidinepropanol, 4-(3-hydroxyphenyl)-3,4-dimethyl-.alpha.-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 14 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:631890 CAPLUS
DOCUMENT NUMBER: 133:222737
TITLE: Preparation of 4-phenyl-4-heteroarylpiperidines as ligands for **opioid** receptors
INVENTOR(S): Liras, Spiros; McHardy, Stanton Furst
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Jpn. Kokai Tokkyo Koho, 34 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000247969	A2	20000912	JP 2000-44911	20000222
EP 1038872	A1	20000927	EP 2000-300974	20000208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

US 6444679 B1 20020903 US 2000-503679 20000214
BR 2000000901 A 20010821 BR 2000-901 20000222
PRIORITY APPLN. INFO.: US 1999-121156P P 19990222
OTHER SOURCE(S): MARPAT 133:222737
GI

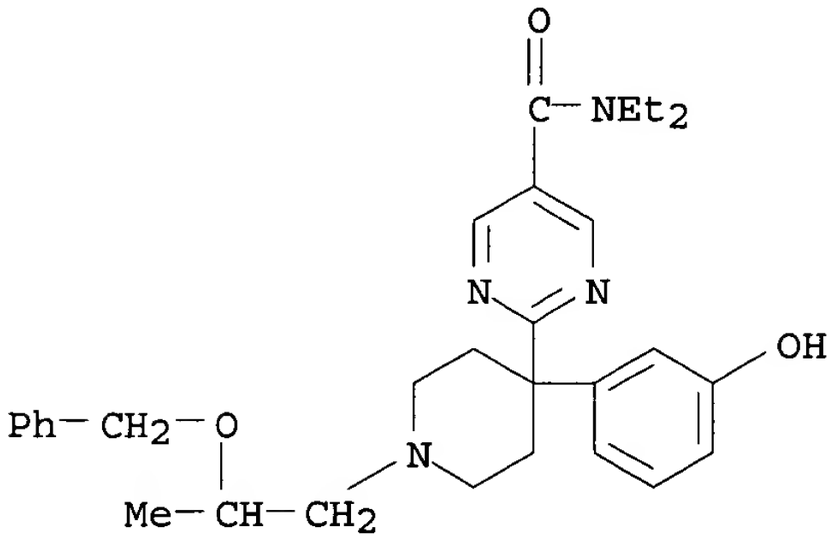


I

AB The title compds. [I; X, Y = O, N, S, CH; provided that the ring contg. X and Y is arom. and both X and Y are not simultaneously O or S; n = 0,1; R1 = H, C0-8 alkoxy-C0-8 alkyl (a total C atoms being .ltoreq.8), aryl, aryl-C1-8 alkyl, heteroaryl, heteroaryl-C1-8 alkyl, heterocyclyl, heterocyclyl-C1-8 alkyl, C3-7 cycloalkyl, C3-7 cycloalkyl-C1-8 alkyl, etc.; R2 = H, aryl, halo, heteroaryl, heterocyclyl, SO2R4, COR4, CONR5R6, CO2R4, C(OH)R5R6, etc.; wherein R4, R5, or R6 is selected from group defined in R1 or R5 and R6 together with bonded N or C atom form 3 to 7-membered ring contg. 0-3 heteroatoms selected from O, N, and S; R3 = HO, hydroxy-C1-6 alkyl, C1-6 alkyl-C1-6 alkoxy, NHSO2R7, C(OH)R7R8, halo, heteroaryl, CONHR7; R7, R8 = H, C1-4 alkyl, C1-4 alkoxy, or C1-4 alkoxy-C1-4 alkyl, wherein each alkyl is optionally substituted with 1-7 F atom(s); Z1 = H,halo, C1-5 alkyl; provided that two-adjacent ring oxygen or nitrogen atoms or ring O atom adjacent to ring S atom do not exist in heterocyclic or heteroaryl portion] are prepd. These compds. regulate bindings to **opioid** receptors and are useful for the improvement, prevention, or treatment of various disorders or conditions, e.g. (1) inflammatory diseases such as arthritis, psoriasis, and asthma, (2) disorders of respiratory function such as asthma, coughing, and apnea (breathlessness), (3) allergy, (4) gastrointestinal disorders such as gastritis, functional intestinal disorders, irritable bowel syndromes, functional diarrhea, functional dilation, functional pain, indigestion not forming peptic ulcer, gastrointestinal motility disorders, and vomiting, (5) stroke, (6) shock, (7) brain edema, (8) brain injury, (9) spinal cord injury, (10) brain ischemia, (11) brain failure suffered after heart bypass or transplant surgery, (12) urinary or reproductive tract disorders including incontinence, (13) chem. dependence or addiction, (14) chronic pain, (15) acute or neurol. pain, (16) systemic lupus erythematosus, (17) Hodgkin's disease, (18) Sjoegren disease, (19) epilepsy, and (20) rejection of organ transplant or skin grafting (no data). Thus, oxidn. of N,N-diethyl-2-[4-(3-hydroxymethylphenyl)-1-(2-methylpentyl)piperidin-4-yl]pyrimidine-5-carboxamide by tetrapropylammonium perruthenate and N-methylmorpholine N-oxide in CH2Cl2 in the presence of 4.ANG. mol. sieve gave an aldehyde which underwent addn. reaction with methylmagnesium bromide in THF at -70.degree. to give N,N-diethyl-2-[4-[3-(1-hydroxyethyl)phenyl]-1-(2-methylpentyl)piperidin-4-yl]pyrimidine-5-carboxamide.

IT **291754-14-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of phenylheteroarylpiperidines as ligands for **opioid** receptors and drugs)

RN 291754-14-8 CAPLUS
CN 5-Pyrimidinecarboxamide, N,N-diethyl-2-[4-(3-hydroxyphenyl)-1-[2-(phenylmethoxy)propyl]-4-piperidinyl]- (9CI) (CA INDEX NAME)



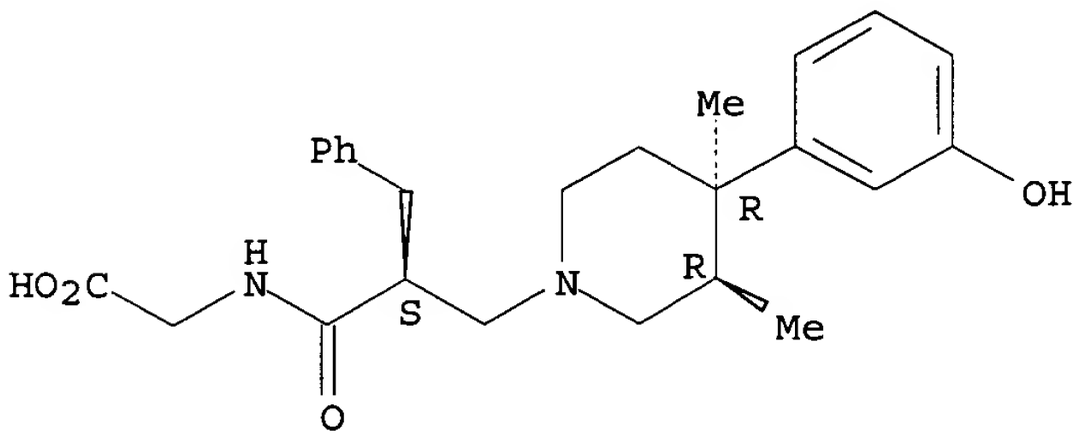
L5 ANSWER 15 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:451987 CAPLUS
DOCUMENT NUMBER: 133:114399
TITLE: ADL-8-2698 (Eli Lilly & Co)
AUTHOR(S): Galligan, James J.
CORPORATE SOURCE: Michigan State University, East Lancing, MI, 48824, USA
SOURCE: Current Opinion in Central & Peripheral Nervous System Investigational Drugs (2000), 2(3), 378-383
CODEN: COCDFA; ISSN: 1464-844X
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 28 refs. ADL-8-2698 (LY-246736) is a potent, peripherally active, .mu. **opioid** receptor antagonist being developed by Adolor and Shire (formerly Roberts Pharmaceuticals), under license from Eli Lilly, as a potential treatment for constipation, post-surgical ileus and irritable bowel syndrome. It is in phase III trials for constipation and phase II trials for post-surgical ileus. Phase II/III trials were initiated for narcotic-induced constipation in Nov. 1999. Shire expects to file an NDA for ADL-8-2698 in 2002. A series of phase I and II studies involving more than 130 volunteers, acute pain patients and chronic **opioid** therapy patients were carried out by Adolor and had been completed and analyzed by Nov. 1999. The results showed that the compd. reversed narcotic-induced constipation and did not reverse narcotic-induced analgesia or ppt. **opioid** withdrawal. ADL-8-2698 was safe and well tolerated with no significant side effects. Phase II trials for post-surgical ileus were initiated by Nov. 1999. ADL-8-2698 does not readily cross the blood-brain barrier. In a mouse model of GI transit ADL-8-2698 antagonized morphine-induced inhibition of GI transit with an ED50 value of 0.46 mg/kg po, with a max. effect at 6 h. ADL-01-0160 (100 mg/kg), a member of the same series, also produced maximal antagonism at 6 h and inhibited transit up to 8 h. With ADL-01-0161 (100 mg/kg), maximal inhibition of transit occurred at 8 h and transit was still inhibited at 24 h, with an ED50 value of 16 mg/kg. No abstinence-induced jumping in mice pretreated with 100 mg/kg morphine, indicating peripheral selectivity. In June 1998, Roberts out-licensed ADL-8-2698 to Adolor in order to accelerate the compd.'s development.

IT **156053-89-3**, LY-246736
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.mu. **opioid** receptor antagonist ADL-8-2698 for treatment of

gastrointestinal disorders)
RN 156053-89-3 CAPLUS
CN Glycine, N-[(2S)-2-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:594935 CAPLUS
DOCUMENT NUMBER: 131:228652
TITLE: Preparation of substituted piperidines for pharmaceutical use as **opioid** antagonists
INVENTOR(S): Carroll, Frank Ivy
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 171 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9945925	A1	19990916	WO 1999-US5131	19990309
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2324418	AA	19990916	CA 1999-2324418	19990309
AU 9930738	A1	19990927	AU 1999-30738	19990309
EP 1061919	A1	20001227	EP 1999-912345	19990309
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002506032	T2	20020226	JP 2000-535340	19990309
US 2002165396	A1	20021107	US 2002-100097	20020319
US 2002169324	A1	20021114	US 2002-100096	20020319
US 2002193602	A1	20021219	US 2002-99948	20020319

PRIORITY APPLN. INFO.:
US 1998-77402P P 19980310
US 1998-107902P P 19981110
WO 1999-US5131 W 19990309
US 2000-623872 A3 20001127

OTHER SOURCE(S): MARPAT 131:228652
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

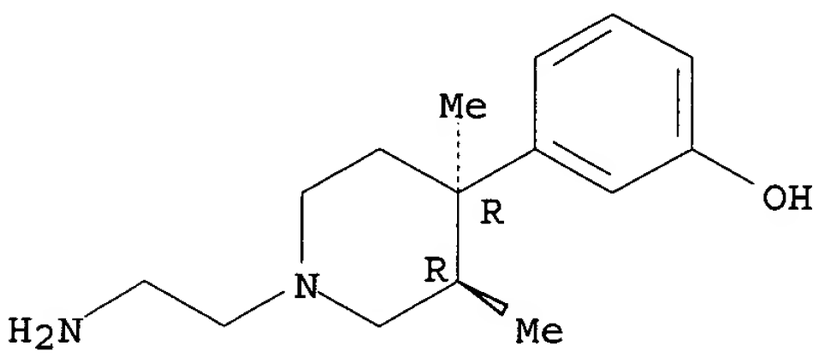
AB Piperidine contg. heterocyclic compds. I [R1, R2 = H, alkyl, aryl, arylalkyl; R3 = alkyl, cycloalkyl, aryl, arylalkyl, etc.], II [R1 = alkyl, arylalkyl; R3, R4, R5, R6 = H, OH, NH2, CN, CF3, CN, NO2, alkyl, alkyloxy, halogen, amino, etc.; R7 = H, alkyl], and III [R1 = alkyl, arylalkyl; R2 = H, NH2, :O, alkyl, arylalkyl, amino, etc.] were prepd. for use as **opioid** antagonists to treat a variety of disease states which involve the **opioid** receptors. Thus, the hydrochloride salt of piperidine IV [R3 = (CH2)2C6H4-4-OH], i.e. RTI 5989-29, was prepd. starting from (+)-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine, N-(tert-butoxycarbonyl)-L-valine, and 3-(4-hydroxyphenyl)propanoic acid. The prepd. heterocyclic compds. contg. a piperidine subunit were tested for .**kappa**.-, .mu.-, and .delta.-**opioid** receptor binding activity.

IT **220122-51-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of heterocyclic compds. contg. a piperidine subunit for pharmaceutical use as **opioid** antagonists)

RN 220122-51-0 CAPLUS

CN Phenol, 3-[(3R,4R)-1-(2-aminoethyl)-3,4-dimethyl-4-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 17 OF 49 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:749847 CAPLUS

DOCUMENT NUMBER: 130:139233

TITLE: Identification of an **Opioid .kappa**. Receptor Subtype-Selective N-Substituent for (+)-(3R,4R)-Dimethyl-4-(3-hydroxyphenyl)piperidine

AUTHOR(S): Thomas, James B.; Fall, Michael J.; Cooper, Julie B.; Rothman, Richard B.; Mascarella, S. Wayne; Xu, Heng; Partilla, John S.; Dersch, Christina M.; McCullough, Karen B.; Cantrell, Buddy E.; Zimmerman, Dennis M.; Carroll, F. Ivy

CORPORATE SOURCE: Chemistry and Life Sciences Research Triangle Institute, Research Triangle Park, NC, 27709, USA

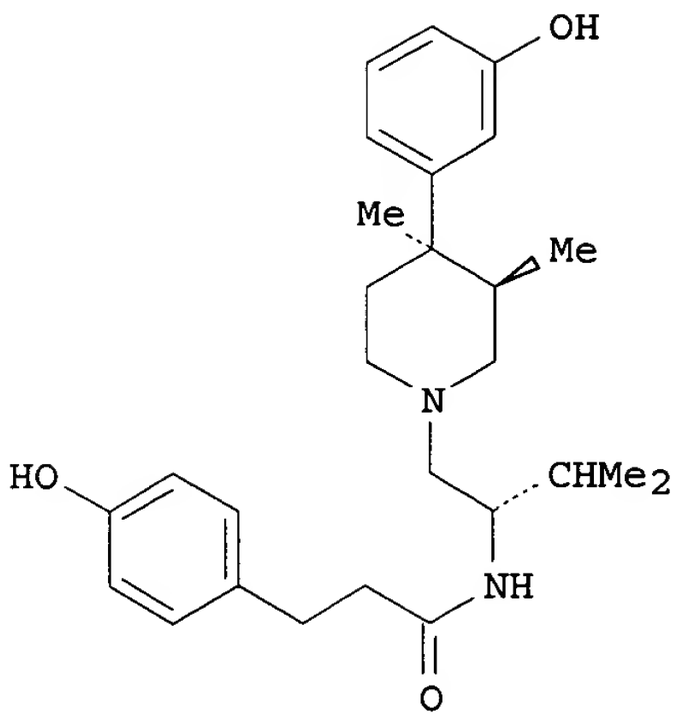
SOURCE: Journal of Medicinal Chemistry (1998), 41(26), 5188-5197
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

09/ 755,021

LANGUAGE: English
GI



I

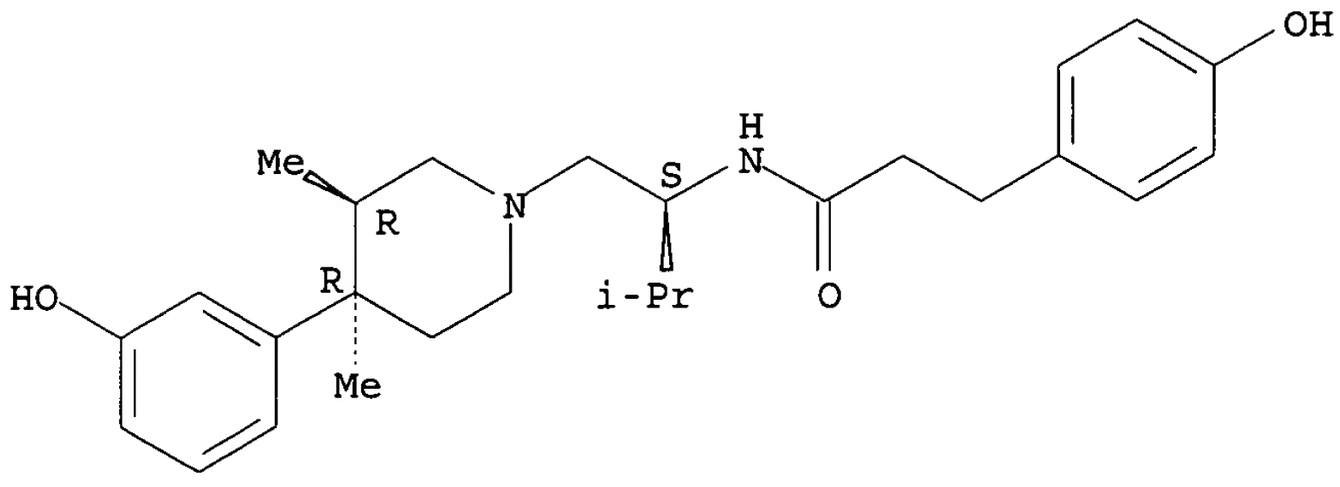
AB A three-component library of compds. was prepd. in parallel using multiple simultaneous soln.-phase synthetic methodol. The compds. were biased toward **opioid** receptor antagonist activity by incorporating (+)-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine (a potent, nonselective **opioid** pure antagonist) as one of the monomers. The other two monomers were N-substituted or unsubstituted Boc-protected amino acids and a range of substituted aryl carboxylic acids and were selected to add chem. diversity. Screening of these compds. in competitive binding expts. with the .**kappa**. **opioid** receptor selective ligand [3H]U69,593 led to the discovery of a novel .**kappa**. **opioid** receptor selective ligand, RTI-5989-29 (I). Addnl. structure-activity relationship studies suggested that I possesses lipophilic and hydrogen-bonding sites that are important to its **opioid** receptor potency and selectivity. These sites appear to exist predominantly within the .**kappa**. receptor since the selectivity arises from a 530-fold loss of affinity of I for the .mu. receptor and an 18-fold increase in affinity for the .**kappa**. receptor relative to the .mu.-selective ligand, (+)-N-[trans-4-phenyl-2-butenyl]-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine. The degree of selectivity obsd. in the radioligand binding expts. was not obsd. in the functional assay. According to its ability to inhibit agonist stimulated binding of [35S]GTP.gamma.S at all three **opioid** receptors, I behaves as a .mu./.**kappa**. **opioid** receptor pure antagonist with negligible affinity for the .delta. receptor.

IT **220122-69-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of an **opioid** antagonist combinatorial library of acylaminoethylpiperidinylphenols)

RN 220122-69-0 CAPLUS

CN Benzenepropanamide, 4-hydroxy-N-[(1S)-1-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl]-, monohydrochloride (9CI) (CA INDEX NAME)

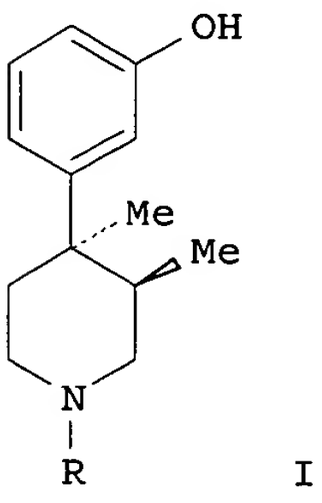
Absolute stereochemistry.



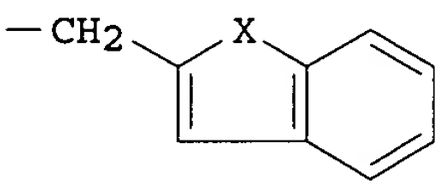
⊙ HCl

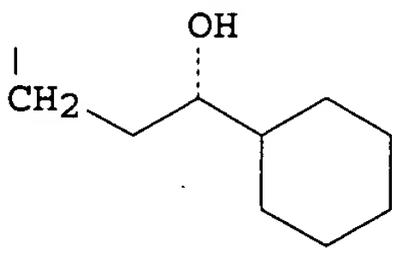
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:270006 CAPLUS
DOCUMENT NUMBER: 128:289744
TITLE: Investigation of the N-Substituent Conformation Governing Potency and .mu. Receptor Subtype-Selectivity in (+)-(3R,4R)-Dimethyl-4-(3-hydroxyphenyl)-piperidine **Opioid** Antagonists
AUTHOR(S): Thomas, James B.; Mascarella, S. Wayne; Rothman, Richard B.; Partilla, John S.; Xu, Heng; McCullough, Karen B.; Dersch, Christina M.; Cantrell, Buddy E.; Zimmerman, Dennis M.; Carroll, F. Ivy
CORPORATE SOURCE: Chemistry and Life Sciences Research Triangle Institute, Research Triangle Park, NC, 27709, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(11), 1980-1990
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

Q= 

Q1= 

AB A study of the binding site requirements assocd. with the N-substituent of (+)-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine (I; R = H) derivs. was undertaken using a set of rigid vs. flexible N-substituents. The study showed that compds. I (R = trans-cinnamyl, trans-2-methylcinnamyl, trans-2-chlorocinnamyl) bearing the trans-cinnamyl N-substituent most closely reproduced the potency at the **opioid** receptor of the

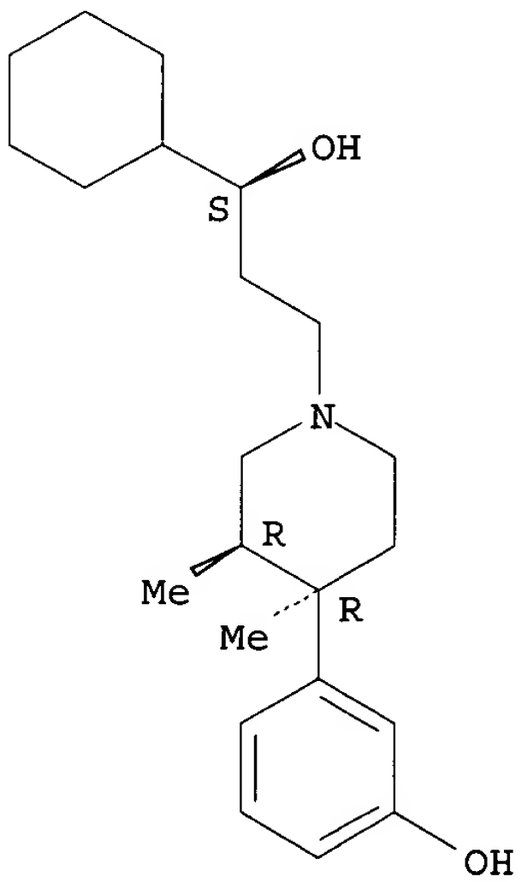
flexible N-propylphenyl or N-propylcyclohexyl analogs previously reported. Neither the N-substituted cis-cinnamyl I (R = cis-cinnamyl), nor the cis-phenylcyclopropylmethyl compds. I (R = cis-2-phenylpropylmethyl), resp., showed high affinity for the **opioid** receptor. However, the N-trans-phenylcyclopropylmethyl compd. I (R = trans-2-phenylcyclopropylmethyl) closely approximated the affinity of compds. I (R = trans-cinnamyl, trans-2-methylcinnamyl, trans-2-chlorocinnamyl). Addnl., the authors found that free rotation of the Ph ring is necessary for high affinity binding and .mu. receptor subtype selectivity as the planar N-substituted thianaphthylmethyl and benzofuranylmethyl compds. I (R = Q, X = S) and I (R = Q, X = O) had significantly lower binding affinities. Altogether, these findings suggest that the high binding affinity, selectivity, and antagonist potency of N-propylphenyl or N-propylcyclohexyl analogs of (+)-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine I (R = H) are achieved via a conformation wherein the connecting chain of the N-substituents is extended away from piperidine nitrogen with the appended ring system rotated out-of-plane relative to the connecting chain atoms. This conformation is quite similar to that obsd. in the solid state for I (R = Q1), as detd. by single crystal X-ray anal. Addnl., it was found that, unlike naltrexone, N-substituents bearing secondary carbons attached directly to the piperidine nitrogen of I (R = H) suffer dramatic losses of potency vs. analogs not substituted in this manner. Using a functional assay which measured stimulation or inhibition of [35S]GTP-.gamma.-S binding, we show that the trans-cinnamyl analogs of (+)-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine I (R = H) retain **opioid** pure antagonist activity and possess picomolar antagonist potency at the .mu. receptor.

IT **119193-09-8**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(investigation of N-substituent conformation in potency and .mu. receptor subtype-selectivity in dimethyl(hydroxyphenyl)piperidine **opioid** antagonists)

RN 119193-09-8 CAPLUS

CN 1-Piperidinepropanol, .alpha.-cyclohexyl-4-(3-hydroxyphenyl)-3,4-dimethyl-, (.alpha.S,3R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 19 OF 49 CAPLUS COPYRIGHT 2003 ACS

09/ 755,021

ACCESSION NUMBER: 1998:8340 CAPLUS
DOCUMENT NUMBER: 128:84404
TITLE: Application of opiate antagonist- and opiate agonist-containing preparations for prophylaxis and therapeutic treatment of migraine and migraine-related illnesses
INVENTOR(S): Bohlen, Heribert
PATENT ASSIGNEE(S): VIVA Diagnostika Diagnostische Produkte G.m.b.H., Germany
SOURCE: Ger. Offen., 10 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19622866	A1	19971211	DE 1996-19622866	19960607
DE 19622866	C2	19981224		
WO 9747293	A1	19971218	WO 1997-EP2823	19970530
W: AU, BR, BY, CA, CN, CZ, FI, HU, IL, JP, KR, MX, NO, NZ, PL, RU, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9730310	A1	19980107	AU 1997-30310	19970530

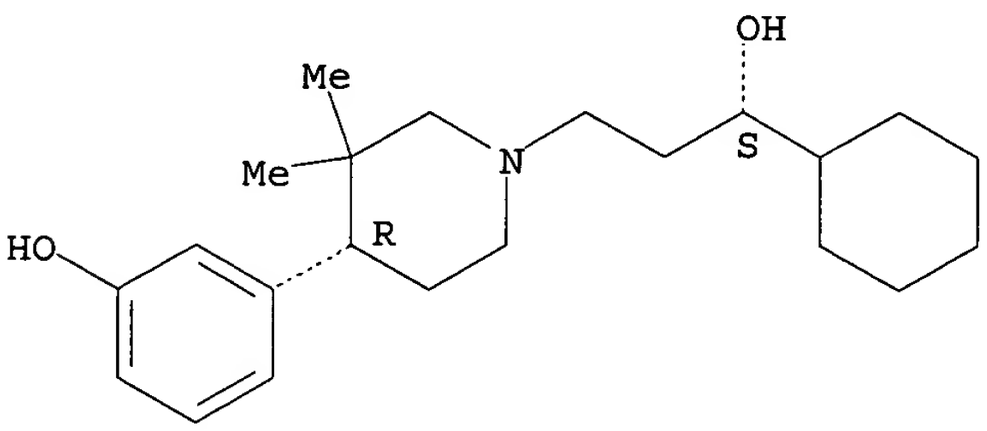
PRIORITY APPLN. INFO.: DE 1996-19622866 19960607
WO 1997-EP2823 19970530

AB Antagonists and agonists of .mu.-, .delta.-, and .**kappa**.-opiate receptors are useful for treatment and prevention of acute or chronic headaches assocd. with migraine or migraine-related illnesses. These agents include piperidines, imidazolines, peptides, pseudopeptides, benzazocines, phenols, and morphinans. The agents are effective even against otherwise therapy-resistant episodic and chronic cluster headaches without side effects or development of tolerance or dependence. They may be administered alone or in combination either simultaneously or sequentially. Thus, naltrexone (2 .times. 50 mg/day orally every other day) completely relieved the pain and other symptoms of a patient's chronic cluster headaches.

IT **200716-15-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opiate antagonist- and agonist-contg. prepns. for prophylaxis and treatment of migraine)

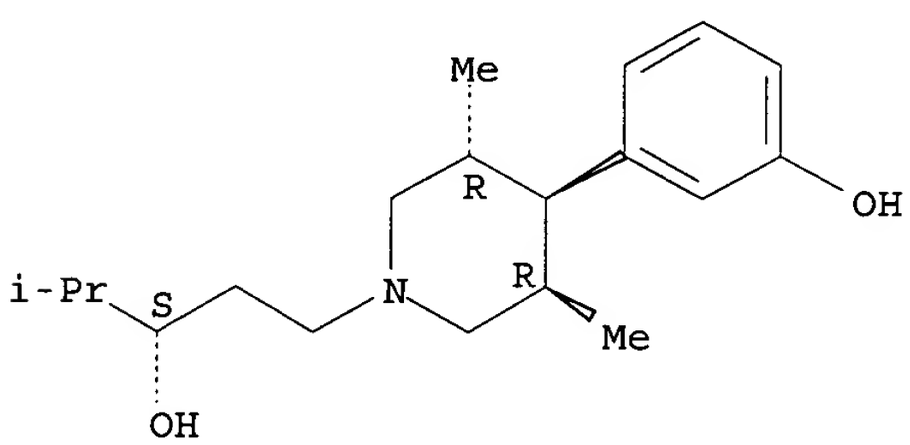
RN 200716-15-0 CAPLUS
CN 1-Piperidinepropanol, .alpha.-cyclohexyl-4-(3-hydroxyphenyl)-3,3-dimethyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 20 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:32031 CAPLUS
DOCUMENT NUMBER: 124:137984
TITLE: The use of topological indices and chemical descriptors basic set in QSAR developments
AUTHOR(S): Catana, C.
CORPORATE SOURCE: Academy of Medical Sciences, Bucharest, 79173, Rom.
SOURCE: Toxicology Modeling (1995), 1(3), 181-9
CODEN: TOMOF8; ISSN: 1354-6724
PUBLISHER: Carfax
DOCUMENT TYPE: Journal
LANGUAGE: English
AB PLS (Partial Least Squares regression) has been valuable method for relating one data matrix, X, to another, Y. Here, PLS method relates the variation in measured biol. activity to the variation in chem. structure between members of a set of similar chem. compds. The usual chem. descriptor variables, matrix X, which includes empirical substituent consts. and phys. detd. descriptors, are partially replaced by topol. indexes and chem. descriptors "basic set". Their utility in PLS is demonstrated in the class of 3,4-dimethyl-4-(3-hydroxyphenyl)piperidines, **opioid** antagonists with potent anorectant activity.
IT **173475-18-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topol. indexes and chem. descriptors use in QSAR developments)
RN 173475-18-8 CAPLUS
CN 1-Piperidinepropanol, 4-(3-hydroxyphenyl)-3,5-dimethyl-.alpha.-(1-methylethyl)-, (3.alpha.,4.alpha.,5.beta.)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L5 ANSWER 21 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:25399 CAPLUS
DOCUMENT NUMBER: 124:87442
TITLE: Synthesis of trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine **opioid** antagonists: application of the cis-thermal elimination of carbonates to alkaloid synthesis
AUTHOR(S): Werner, John A.; Cerbone, Louis R.; Frank, Scott A.; Ward, Jeffrey A.; Labib, Parviz; Tharp-Taylor, Roger W.; Ryan, C. W.
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285-4813, USA
SOURCE: Journal of Organic Chemistry (1996), 61(2), 587-97
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 124:87442

09/ 755,021

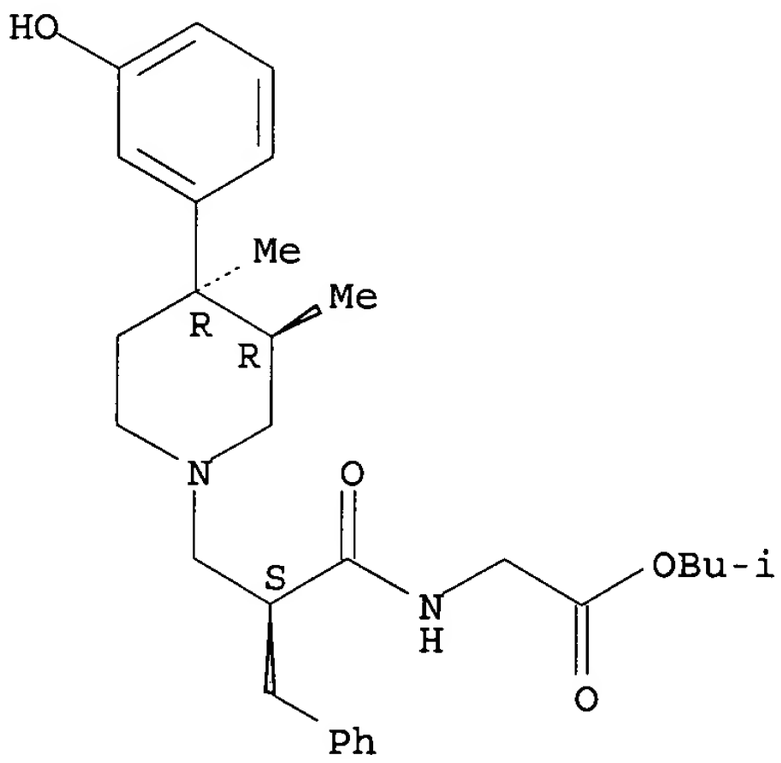
AB Improved syntheses of two trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine **opioid** antagonists from 1,3-dimethyl-4-piperidinone are described. 1,3-Dimethyl-4-(3-isopropoxyphenyl)-piperidinol was selectively dehydrated in a two step process to the 1,3-dimethyl-4-(3-isopropoxyphenyl)-1,2,3,6-tetrahydropyridine (I) by the cis-thermal elimination of the corresponding alkyl carbonate deriv. at 190 .degree.C. In the presence of a basic nitrogen, the success of the elimination was found to be critically dependent upon the nature of the carbonate alkyl group, with Et, i-Bu, and i-Pr being preferred (90% yield). Alkylation of the metalloenamine, formed by deprotonation of I with n-BuLi, proceeded regio- and stereospecifically to give trans-3,4-dimethyl-4-(3-isopropoxyphenyl)-1,2,3,4-tetrahydropyridine, which was converted in three steps to the common intermediate, (3R,4R)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine. LY255582, a centrally-active **opioid** antagonist, and LY246736-dihydrate, a peripherally-active **opioid** antagonist, were prepd. from 1,3-dimethyl-4-piperidinone in 11.8% yield (8 steps) and 6.2% yield (12 steps), resp.

IT **145603-86-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of (hydroxyphenyl)piperidine **opioid** antagonists via thermal elimination of carbonates)

RN 145603-86-7 CAPLUS

CN Glycine, N-[(2S)-2-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-, 2-methylpropyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 22 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:907624 CAPLUS
DOCUMENT NUMBER: 123:313767
TITLE: Preparation of 3,4,4-trisubstituted piperidinyl N-alkylcarboxylates and intermediates, useful as **opioid** antagonists.
INVENTOR(S): Frank, Scott Alan; Prather, Douglas Edward; Ward, Jeffrey Alan; Werner, John Arnold
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA
SOURCE: Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

09/ 755,021

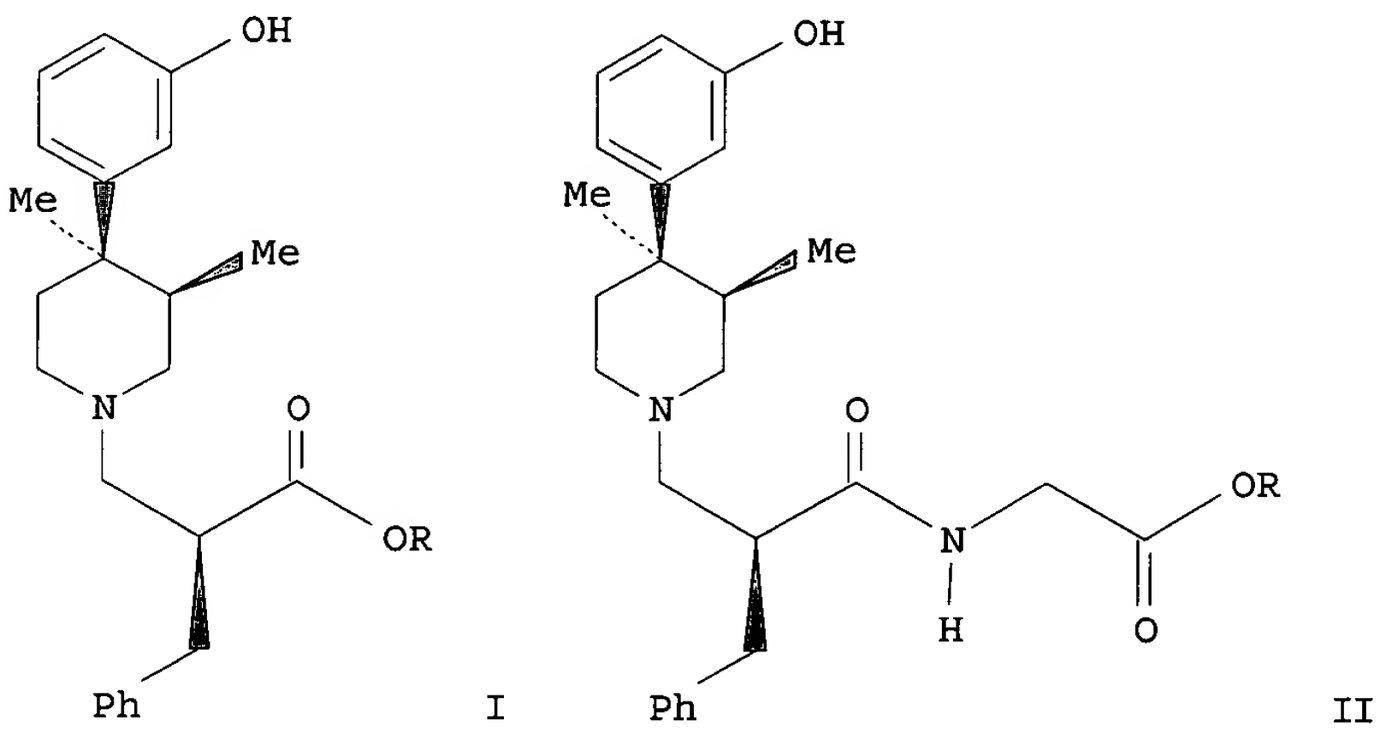
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 657428	A1	19950614	EP 1994-308951	19941202
EP 657428	B1	20010404		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5434171	A	19950718	US 1993-164074	19931208
AU 9479170	A1	19950615	AU 1994-79170	19941201
AU 681198	B2	19970821		
JP 07215937	A2	19950815	JP 1994-298356	19941201
ZA 9409584	A	19960603	ZA 1994-9584	19941201
IL 111843	A1	20000229	IL 1994-111843	19941201
PL 181734	B1	20010928	PL 1994-306068	19941201
CZ 290559	B6	20020814	CZ 1994-2992	19941201
CA 2137221	AA	19950609	CA 1994-2137221	19941202
FI 9405703	A	19950609	FI 1994-5703	19941202
NO 9404644	A	19950609	NO 1994-4644	19941202
BR 9404842	A	19950808	BR 1994-4842	19941202
HU 71489	A2	19951128	HU 1994-3466	19941202
RU 2145958	C1	20000227	RU 1994-42903	19941202
EP 984004	A2	20000308	EP 1999-203390	19941202
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT				
AT 200279	E	20010415	AT 1994-308951	19941202
ES 2155844	T3	20010601	ES 1994-308951	19941202
CN 1111239	A	19951108	CN 1994-119376	19941203
CN 1057294	B	20001011		
CN 1223257	A	19990721	CN 1998-123069	19981203
FI 2000000353	A	20000217	FI 2000-353	20000217

PRIORITY APPLN. INFO.: US 1993-164074 A 19931208
EP 1994-308951 A3 19941202

OTHER SOURCE(S): CASREACT 123:313767; MARPAT 123:313767

GI



AB The invention relates to novel cryst. compds. I and II [R = C1-6 alkyl] and their salts, as well as processes for their prepn., and their use as intermediates and/or peripheral **opioid** antagonists. The HCl, HBr, succinate, and (+)-dibenzoyltartrate salts of I are stable, cryst., and when contaminated by the undesired (R,R,R) epimer, undergo diastereomeric enrichment by crystn. II.2H2O (R = H) and certain assocn. compds. of II (R = C1-6 alkyl), specifically the HCl-acetone solvate and the 1:1 and 3:2 malates, are useful for treatment of irritable bowel

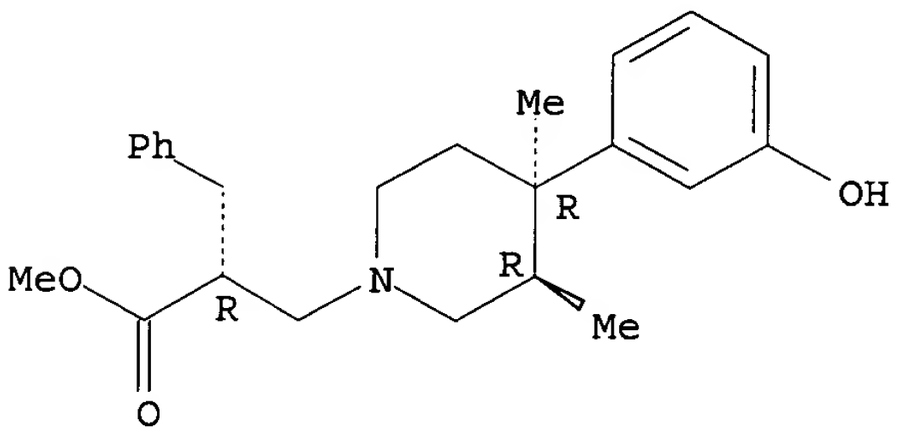
syndrome, idiopathic constipation, and non-ulcer dyspepsia. For example, condensation of I (R = H) with p-MeC6H4SO3H.H2NCH2CO2Bu-iso using DCC, HOBt, and Et3N in THF gave 95% II (R = Bu-iso). Hydrolysis of the latter compd. using NaOH in aq. EtOH at 25-30.degree., followed by neutralization and crystn. at pH 6.0, gave II.2H2O (R = H) in 85% yield. Compds. II had AD50 of > 8 mg/kg in the morphine-inhibited mouse writhing test, but ED50 of < 1 mg/kg in the mouse diarrhea test, indicating greater relative antagonism of peripheral **opioid** effects than central activity.

IT **170098-42-7P**
RL: BYP (Byproduct); PREP (Preparation)
(byproduct; prepn. of piperidinyl alkylcarboxylates as **opioid** antagonists)

RN 170098-42-7 CAPLUS

CN 1-Piperidinepropanoic acid, 4-(3-hydroxyphenyl)-3,4-dimethyl-.alpha.-(phenylmethyl)-, methyl ester, hydrochloride, [3R-[1(R*),3.alpha.,4.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



○ HCl

L5 ANSWER 23 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:821489 CAPLUS
DOCUMENT NUMBER: 123:246015
TITLE: Disposition of the **opioid** antagonist, LY255582, in rats and dogs
AUTHOR(S): Swanson, Steven P.; Catlow, John; Pohland, Raymond C.; Chay, Sylvia H.; Johnson, Ted
CORPORATE SOURCE: Dep. Drug Metab. & Disposition, Eli Lilly & Co., Indianapolis, IN, 46285, USA
SOURCE: Drug Metabolism and Disposition (1995), 23(9), 916-21
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

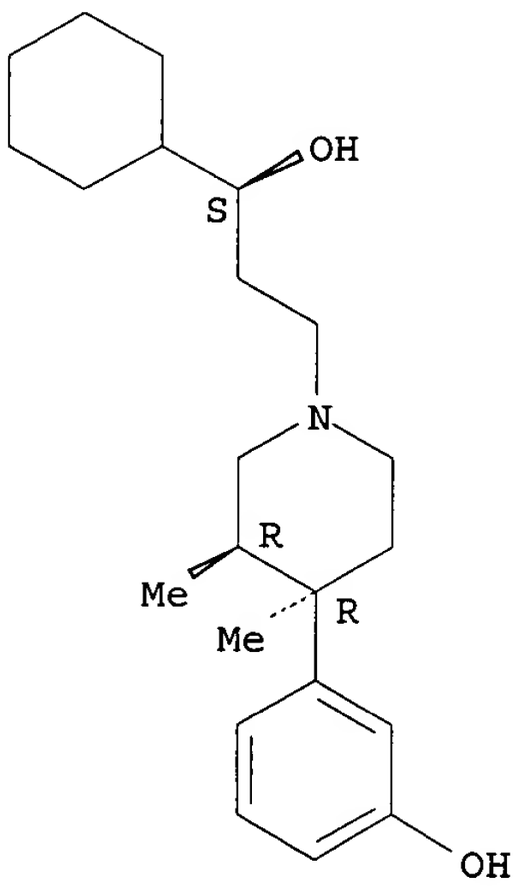
AB LY255582 is a phenylpiperidine **opioid** antagonist under development as an appetite suppressant and for the treatment of obesity. Female beagles were administered [14C]LY255582 at dosages of 0.72 mg/kg i.v. or 7.2 mg/kg orally. The majority (54-58%) of the radioactivity was eliminated in the urine over 8 days after both oral and i.v. drug administration, primarily as polar metabolites. Peak plasma levels of parent drug in the dog were 11.5 and 311 ng/mL after oral and i.v. administration, resp., and declined with a half-life of 3.2 h. Peak plasma levels of LY255582 in the rat were 7.9 and 160 ng/mL after administration of [14C]LY255582 at dosages of 35 mg/kg orally and 1 mg/kg i.v., resp. The half-life of parent drug in rats was 1.5 h; however, the terminal half-lives of radioactivity equiv. were 7.9 and 31.7 h after i.v. and oral administration, resp. The bioavailability of parent LY255582 was

<1% in both the rat and the dog, primarily because of extensive first-pass metabol. Whole-body autoradiog. studies in rats after administration of a single oral 35 mg/kg dose of [14C]LY255582 at dosages of 35 mg/kg orally and 1 mg/kg i.v., resp. The half-life of parent drug in rats was 1.5 h; however, the terminal half-lives of radioactivity equiv. were 7.9 and 31.7 h after i.v. and oral administration, resp. The bioavailability of parent LY255582 was <1% in both the rat and the dog, primarily because of extensive first-pass metab. Whole-body autoradiog. studies in rats after administration of a single oral 35 mg/kg dose of [14C]LY255582 indicated that radioactivity was rapidly absorbed and distributed throughout the body. Radioactivity concd. in the liver and was eliminated slowly. Little or no parent drug was eliminated in the urine of either species. As in the urine, the major residues present in the liver and bile of rats orally administered [14C]LY255582 were uncharacterized polar metabolites with little parent drug present.

IT **119193-09-8**, LY255582
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(disposition of the **opioid** antagonist, LY255582, in rats and dogs)

RN 119193-09-8 CAPLUS
CN 1-Piperidinepropanol, .alpha.-cyclohexyl-4-(3-hydroxyphenyl)-3,4-dimethyl-, (.alpha.S,3R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 24 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:809796 CAPLUS
DOCUMENT NUMBER: 123:275726
TITLE: **Opioid** peptide receptor studies. 3. Interaction of **opioid** peptides and other drugs with four subtypes of the .**kappa**.2 receptor in guinea pig brain
AUTHOR(S): Ni, Qing; Xu, Heng; Partilla, John S.; de Costa, Brian R.; Rice, Kenner C.; Kayakiri, Hiroshi; Rothman, Richard B.
CORPORATE SOURCE: Clinical Psychopharmacology Section, Baltimore, MD, 21224, USA
SOURCE: Peptides (Tarrytown, New York) (1995), 16(6), 1083-95
CODEN: PPTDD5; ISSN: 0196-9781

09/ 755,021

PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

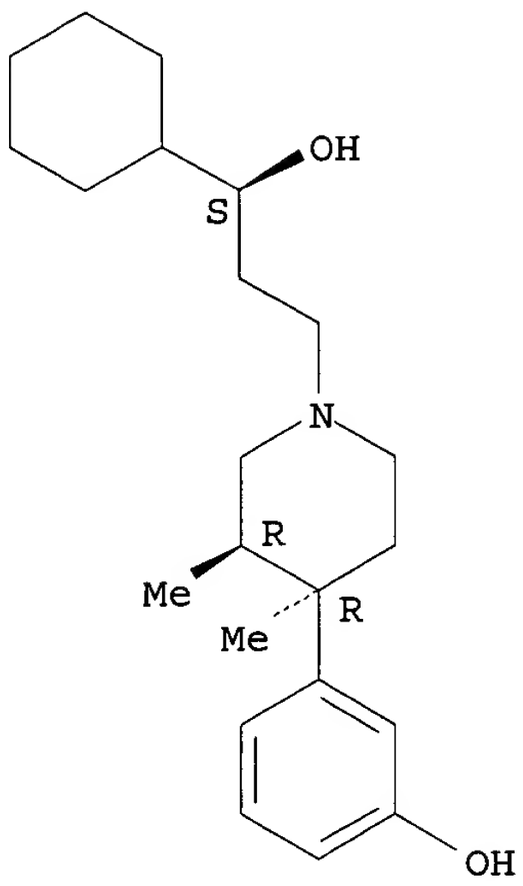
AB Using guinea pig, rat, and human brain membranes depleted of .mu. and .delta. receptors by pretreatment with the site-directed acylating agents BIT (.mu. selective) and FIT (.delta. selective), previous studies from our lab. resolved two subtypes of the .**kappa**.2 binding site, termed .**kappa**.2a and .**kappa**.2b. In more recent studies, we used 6.beta.-[125Iodo]-3,14-dihydroxy-17-cyclopropylmethyl-4,5.alpha.-epoxymorphinan ([125I]IOXY) to characterize multiple .**kappa**.2 binding sites in rat brain. The results indicated that [125I]OXY, like [3H]bremazocine, selectively labels .**kappa**.2 binding sites in rat brain membranes pretreated with BIT and FIT. In the rat brain, using 100 nM [D-Ala2-MePhe4,Gly-ol5]enkephalin to block [125I]IOXY binding to the .**kappa**.2b site, we resolved two subtypes of the .**kappa**.2a binding site. In the present study we examd. the binding of [125I]OXY to the .**kappa**.2 receptors of guinea pig brain. As obsd. in rat brain, [125I]IOXY, under appropriate assay conditions, selectively labels .**kappa**.2 binding sites. Quant. binding studies readily demonstrated the presence of .**kappa**.2a and .**kappa**.2b binding sites. The .**kappa**.2a binding sites were selectively assayed using 5 .mu.M [Leu5]enkephalin to block [125I]IOXY binding to the .**kappa**.2b sites, and .**kappa**.2b sites were selectively assayed using 5 .mu.M (-)-(1S,2S)-U50,488 to block [125I]IOXY binding to the .**kappa**.2a sites. Under these conditions, two subtypes of the .**kappa**.2a site were resolved with high (.**kappa**.2a-1) and low (.**kappa**.2a-2) affinity for nor-BNI (K1 values = 0.88 and 476 nM) and CI977 (Ki values = 17.5 and 95.098 nM). Similarly, two subtypes of the .**kappa**.2b site were obsd. with high (.**kappa**.2b-1) and low (.**kappa**.2b-2) affinity for [D-Ala2-MePhe4,Gly-ol5]enkephalin (DAMGO) (K1 values = 97 and 12.321 nM) and .alpha.-neoendorphin (K1 values = 33 and 5308 nM). Two-site models were also resolved in the presence of 100 .mu.M 5'-guanylyimidodiphosphate (GppNHp). We carried out detailed ligand selectivity anal. of the multiple .**kappa**.2 binding sites. Most test agents were either nonselective or selective for the .**kappa**.2a-1 site. Nalbuphine was moderately selective for the .**kappa**.2a site. Similarly, although most test agents were either nonselective or selective for the .**kappa**.2b-1 site, butorphanol, and the delta antagonists naltrindole, naltriben, and 7-benzylidene-7-dehydronaltrexone were moderately selective for the .**kappa**.2b-2 site. Of the endogenous **opioid** peptides tested, BAM22P had the highest affinity for the .**kappa**.2b-2 site (31 nM) and peptide E had the highest affinity for the .**kappa**.2a-2 binding site (53 nM). These data provide addnl. evidence for heterogeneity of the .**kappa**.-**opioid** receptor and new targets for drug design, synthesis, and therapeutics.

IT **119193-09-8**, LY 255582
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. anal. of .**kappa**.2a and .**kappa**.2b receptors of brain)

RN 119193-09-8 CAPLUS

CN 1-Piperidinepropanol, .alpha.-cyclohexyl-4-(3-hydroxyphenyl)-3,4-dimethyl-, (.alpha.S,3R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 25 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:792484 CAPLUS
DOCUMENT NUMBER: 123:218718
TITLE: Ligand selectivity of cloned human and rat **opioid** Mu receptors
AUTHOR(S): Brothman, Richard B.; Xu, Heng; Wang, Jia Bei; Partilla, John S.; Kayakiri, Hiroshi; Rice, Kenner C.; Uhl, George R.
CORPORATE SOURCE: Clinical Psychopharmacology Section, Laboratory of Medicinal Chemistry, Baltimore, MD, 21224, USA
SOURCE: Synapse (New York) (1995), 21(1), 60-4
CODEN: SYNAET; ISSN: 0887-4476
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

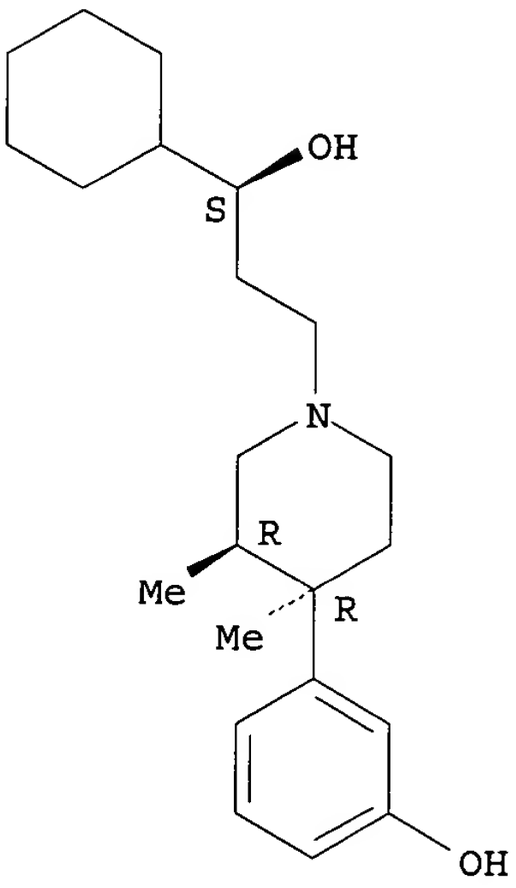
AB Opiate receptors play major roles in analgesic and euphoric effects of opiate drugs. Recent cloning of cDNAs encoding the rodent and human .mu. receptor revealed high homol. between the predicted receptors but also some sequence differences. To det. if these sequence differences produced significant changes in ligand-selectivity profiles, the authors assessed these profiles in expressing COS and CHO cell lines using the agonist ligand [125I]IOXY-AGO (5.beta.-[125Iodo]-3,14-dihydroxy-17-methyl-4-5.alpha.-epoxymorphinan). This ligand's high specific activity (2200 Ci/mmol) and high affinity for .mu. **opioid** receptors generated high signal-to-noise ratio binding. The resulting ligand-selectivity profiles of the human and rat .mu. receptors reveal modest differences in affinities for morphine and naloxone in COS cells but not CHO cells. Ligand-selectivity profiles of the rat and human .mu. receptors were otherwise similar. Interesting differences between these data and data previously obtained with the peptide agonist [3H]DAMGO suggest that the peptide and alkaloid agonists may label different domains of the .mu. receptor.

IT **119193-09-8**, LY 255582
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cloned human and rat **opioid** .mu.-receptor ligand selectivity)

RN 119193-09-8 CAPLUS
CN 1-Piperidinepropanol, .alpha.-cyclohexyl-4-(3-hydroxyphenyl)-3,4-dimethyl-

, (.alpha.S,3R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 26 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:548200 CAPLUS
DOCUMENT NUMBER: 121:148200
TITLE: use of the mouse vas deferens to determine .mu., .delta., and .**kappa**. receptor affinities of **opioid** antagonists
AUTHOR(S): Cohen, Marlene L.; Mendelsohn, Laurane G.; Mitch, Charles H.; Zimmerman, Dennis M.
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Receptor (1994), 4(1), 43-53
CODEN: RECEE5; ISSN: 1052-8040
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study was designed to identify a single smooth muscle prepn. possessing .mu., .delta., and .**kappa**. receptors that can be used in the development of **opioid** selective antagonists. In vitro studies with the mouse vas deferens indicated that the .delta. selective agonists, DPLPE and DSLET, had potent agonist activity (ED50 .apprxeq.1 nM) to inhibit the twitch response. The .mu. selective agonists, normorphine and fentanyl, also inhibited the twitch response in the mouse vas deferens, but were approx 100-fold less potent than the .delta. selective agonists, consistent with the enrichment of this prepn. with .delta. receptors. U50,488, a .**kappa**. selective agonist, also inhibited the twitch response with a potency similar to that of the .mu. agonists. Naloxone, MR 2266, and WIN 44,441 all antagonized the agonist activity of U50,488 with antagonist dissocn. consts. distinct from those calcd. using .mu. or .delta. receptor agonists. To confirm the presence of all three **opioid** receptors in this prepn., the authors examd. a series of 14 phenylpiperidine **opioid** antagonists. An excellent correlation was obsd. between affinities of these piperidine **opioid** antagonists at .mu. and .**kappa**. receptors detd. via radioligand binding studies, and affinities detd. by blockade of fentanyl- or U50,488-induced twitch inhibition. Of the piperidine **opioid** antagonists studied, two possessed relatively high .**kappa**. receptor antagonist affinity. Furthermore, the study of an

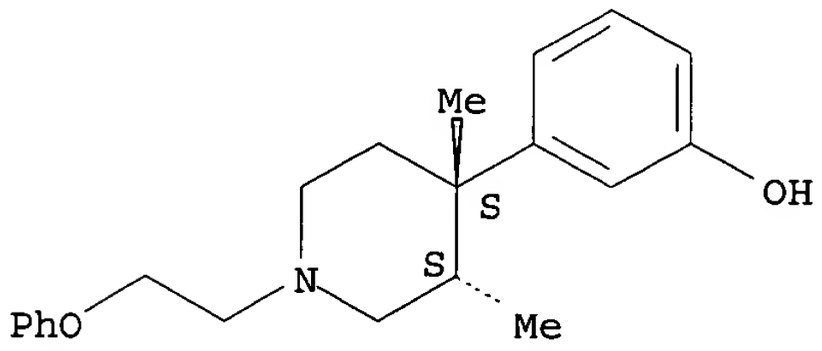
enantiomeric pair of an N-substituted 4-phenylpiperidine deriv. demonstrated differences in abs. configuration to be more important for binding at .mu. and .delta. than .**kappa**. receptors. Thus, the authors have established the presence of .**kappa**., in addn. to the known .mu. and .delta. receptors, in the mouse vas deferens, and identified certain piperidines to have high .**kappa**. receptor antagonist affinity.

IT **149710-92-9**, LY 256822
RL: ANST (Analytical study)
(.mu. and .delta. and **.kappa.** receptor affinities of, mouse vas deferens for detg., as **opioid** antagonist)

RN 149710-92-9 CAPLUS

CN Phenol, 3-[(3R,4R)-3,4-dimethyl-1-(2-phenoxyethyl)-4-piperidinyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L5 ANSWER 27 OF 49 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:457300 CAPLUS

DOCUMENT NUMBER: 121:57300

TITLE: Discovery of a potent, peripherally selective trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine **opioid** antagonist for the treatment of gastrointestinal motility disorders

AUTHOR(S): Zimmerman, Dennis M.; Gidda, Jaswant S.; Cantrell, Buddy E.; Schoepp, Darryle D.; Johnson, Bryan G.; Leander, J. David

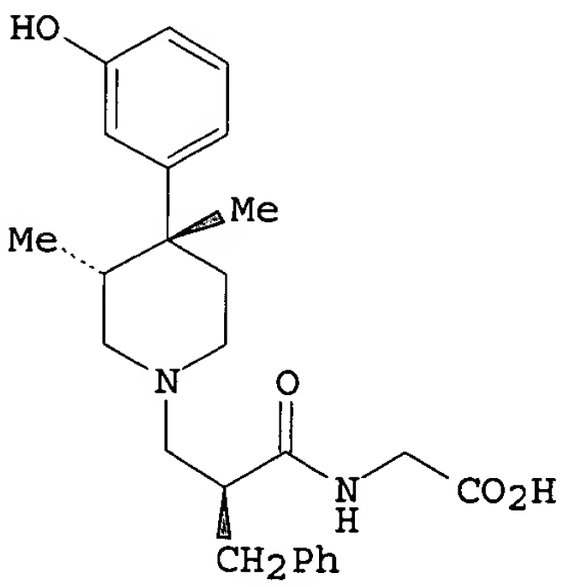
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA

SOURCE: Journal of Medicinal Chemistry (1994), 37(15), 2261-5
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



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09/ 755,021

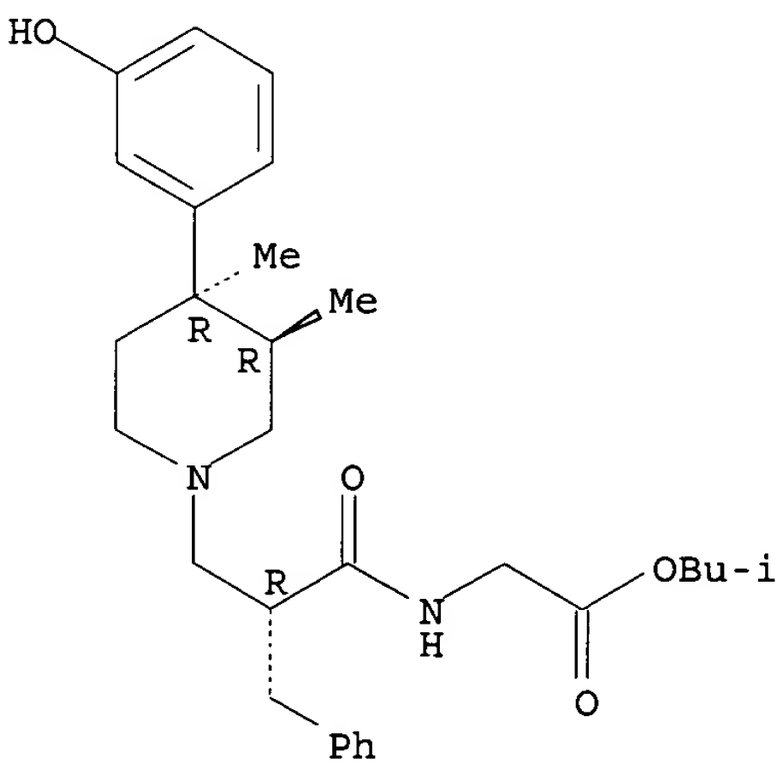
AB Structure-activity relationship studies were pursued within N-substituted-trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines in an effort to discover a peripherally selective **opioid** antagonist with high activity following systemic administration. Altering the size and the polarity of the N-substituent led to the discovery of I (LY246736). I has high affinity for **opioid** receptors (Ki = 0.77, 40, and 4.4 nM for .mu., .**kappa**., and .delta. receptors, resp.). It is a potent .mu. receptor antagonist following parenteral and oral administration and distributes selectively (>200-fold selectivity) to peripheral receptors. Thus, I has properties suitable for the clin. investigation of .mu. **opioid** receptor involvement in GI motility disorders.

IT **145590-95-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and **opioid** antagonist activity of)

RN 145590-95-0 CAPLUS

CN Glycine, N-[(2R)-2-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-, 2-methylpropyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 28 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:520 CAPLUS
DOCUMENT NUMBER: 120:520
TITLE: Long-term treatment of obese Zucker rats with LY255582 and other appetite suppressants
AUTHOR(S): Shaw, Walter N.
CORPORATE SOURCE: Lilly Res. Lab., Indianapolis, IN, 46825, USA
SOURCE: Pharmacology, Biochemistry and Behavior (1993), 46(3), 653-9
CODEN: PBBHAU; ISSN: 0091-3057
DOCUMENT TYPE: Journal
LANGUAGE: English

AB LY255582, administered s.c., decreased food intake and body wt. gain of fed obese Zucker rats during the entire 30-day period of treatment. No tolerance to these biol. effects of LY255582 could be demonstrated. D-amphetamine and naltrexone, administered s.c., and d,l-fenfluramine and salbutamol, administered orally, decreased food intake for .ltoreq.6 to 12 days, in contrast to the long-lasting effects of LY255582. Sulbutamol suppressed the appetite of obese rates for 3-4 days only. After an addnl.

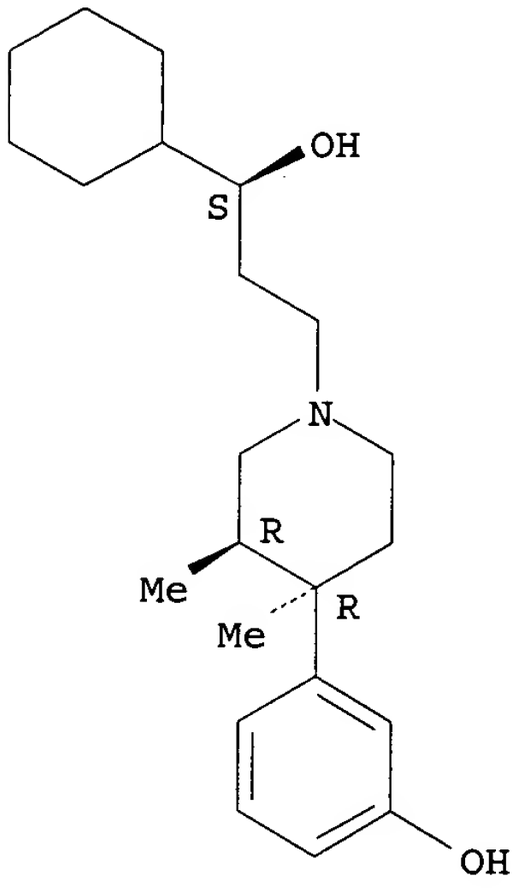
12 days of treatment, wt. gain was decreased accompanied by no appetite suppression. Thus, there is a difference in the duration of action of the **opioid** antagonist, LY255582, when compared to amphetamine, fenfluramine, naltrexone, and salbutamol, on food intake and body wt. gain of obese rats.

IT **119193-09-8**, LY255582
RL: BIOL (Biological study)
(appetite-suppressant activity of, obesity treatment with)

RN 119193-09-8 CAPLUS

CN 1-Piperidinepropanol, .alpha.-cyclohexyl-4-(3-hydroxyphenyl)-3,4-dimethyl-, (.alpha.S,3R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 29 OF 49 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1993:649813 CAPLUS

DOCUMENT NUMBER: 119:249813

TITLE: 3,4-Dimethyl-4-(3-hydroxyphenyl)piperidines: **opioid** antagonists with potent anorectant activity

AUTHOR(S): Mitch, Charles H.; Leander, J. David; Mendelsohn, Laurane G.; Shaw, Walter N.; Wong, David T.; Cantrell, Buddy E.; Johnson, Bryan G.; Reel, John K.; Snoddy, John D.; et al.

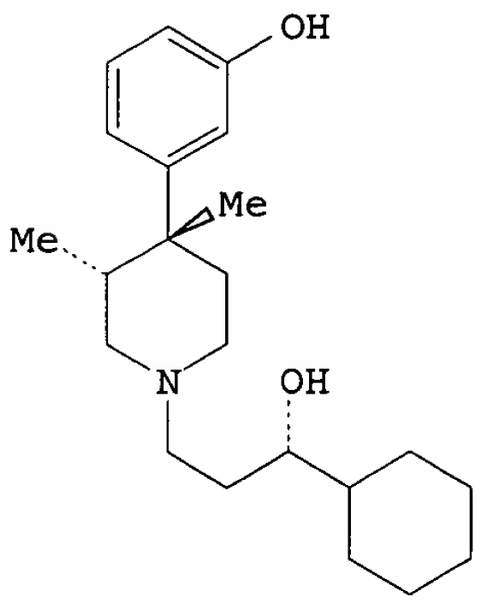
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA

SOURCE: Journal of Medicinal Chemistry (1993), 36(20), 2842-50
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



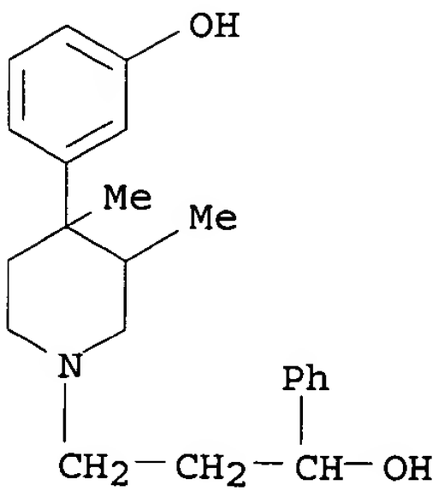
I

AB A series of (3*,4R*)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine **opioid** antagonists with varying substituents on the nitrogen were evaluated for their effect on food consumption in obese Zucker rats. **Opioid** affinity (.mu., .**kappa**., and .delta. for selected compds.) and **opioid** antagonist activity (.mu. and .**kappa**. were characterized) and compared to effects on food consumption. No compds. with high selectivity for either (.mu. or .**kappa**. receptors were discovered. However, compds. in the series had exceptional potency as **opioid** antagonists and in reducing food consumption in the obese Zucker rat. In contrast, a few compds. with high potency as **opioid** antagonists had much weaker potency for inhibiting food consumption. (3R,4R)-3,4-Dimethyl-1-[(3S)-3-hydroxy-3-cyclohexylpropyl]-4-(3-hydroxyphenyl)piperidine (LY255582) (I) emerged as having the best activity profile, both in reducing food consumption and as an **opioid** antagonist. Compd. I is a highly potent .mu., .**kappa**.-, and .delta.-**opioid** antagonist with possible clin. utility as an appetite suppressant for wt. loss.

IT **59381-87-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and **opioid** antagonist and anorectant activity of)

RN 59381-87-2 CAPLUS

CN 1-Piperidinepropanol, 4-(3-hydroxyphenyl)-3,4-dimethyl-.alpha.-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

L5 ANSWER 30 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:573579 CAPLUS

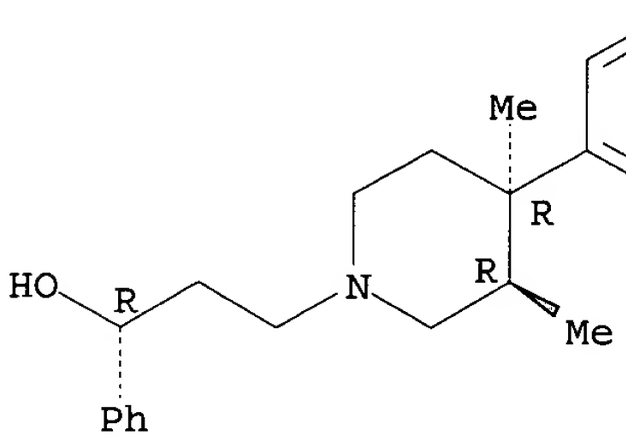
09/ 755,021

DOCUMENT NUMBER: 119:173579
TITLE: Structure-activity relationships of trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine antagonists for .mu.- and .**kappa**.-**opioid** receptors
AUTHOR(S): Zimmerman, Dennis M.; Leander, J. David; Cantrell, Buddy E.; Reel, Jon K.; Snoddy, John; Mendelsohn, Laurane G.; Johnson, Bryan G.; Mitch, Charles H.
CORPORATE SOURCE: CNS Div., Lilly Res. Lab., Indianapolis, IN, 46285, USA
SOURCE: Journal of Medicinal Chemistry (1993), 36(20), 2833-41
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of racemic N-substituted trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines were evaluated for **opioid** agonist and antagonist activity at .mu. and .**kappa**. receptors. Several highly potent .mu. and .**kappa**. antagonists were discovered; however, no compds. with high selectivity for either the .mu. or .**kappa**. receptor were identified. Importantly, no deriv. was found to have significant **opioid** agonist activity. Two derivs. were resolved, and the activities of the enantiomers were investigated. Only a limited stereochem. effect on **opioid** receptor selectivities was obsd. The structure-activity relationships described establish the existence of an important lipophilic binding site distal to the nitrogen for both .mu. and .**kappa**. receptors and confirm the pure **opioid** antagonist pharmacophore nature of the trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine structure.

IT **149710-62-3**
RL: BIOL (Biological study)
(.mu.- and .**kappa**.-**opioid** antagonist activity of, structure in relation to)
RN 149710-62-3 CAPLUS
CN 1-Piperidinepropanol, 4-(3-hydroxyphenyl)-3,4-dimethyl-.alpha.-phenyl-, (.alpha.R,3R,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



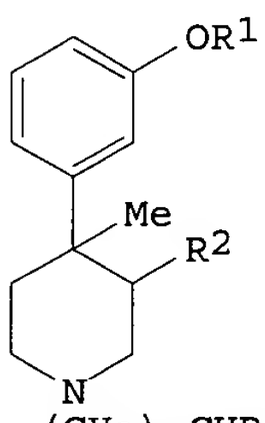
L5 ANSWER 31 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:539107 CAPLUS
DOCUMENT NUMBER: 119:139107
TITLE: Preparation of phenylpiperidine derivatives as peripheral **opioid** antagonists.
INVENTOR(S): Cantrell, Buddy E.; Zimmerman, Dennis M.
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA
SOURCE: Can. Pat. Appl., 157 pp.
CODEN: CPXXEB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

09/ 755,021

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2064373	AA	19920930	CA 1992-2064373	19920327

PRIORITY APPLN. INFO.: US 1991-667042 19910329
OTHER SOURCE(S): MARPAT 119:139107
GI



(CH2)nCHR3COA I

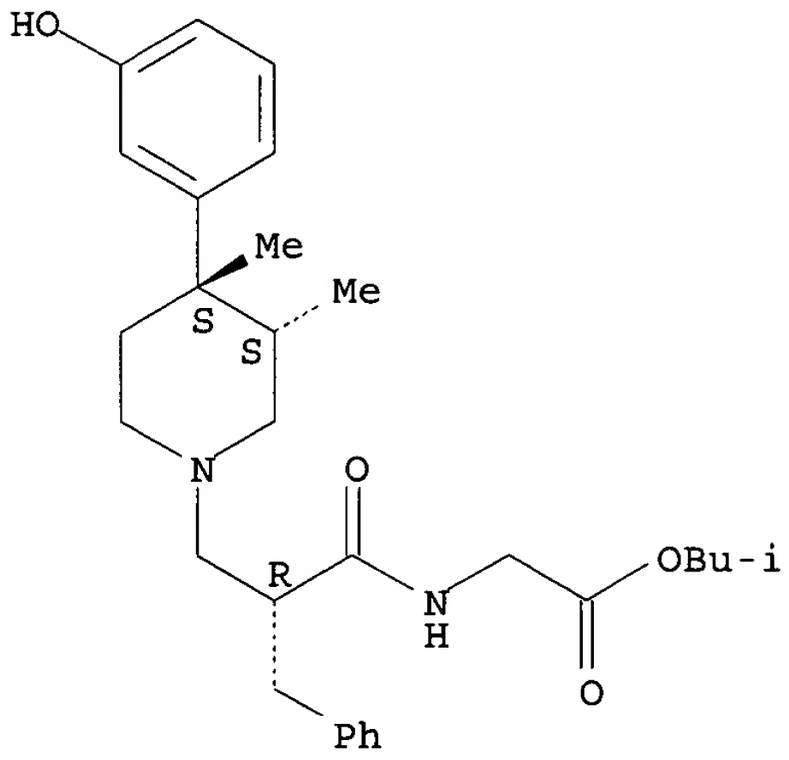
AB Title compds. I (R1 = H, C1-5 alkyl; R2 = H, C1-5 alkyl, C2-6 alkenyl; R3 = H, C1-10 alkyl, C3-10 alkenyl, Ph, phenyl-C1-3-alkyl, cycloalkyl, C5-8 cycloalkenyl, etc.; A = R4O, R6R5N wherein R4 = H, C1-10 alkyl, C2-10 alkenyl, cycloalkyl, C5-8 cycloalkenyl, etc.; R5 = H, C1-3 alkyl; R6 = H, C1-10 alkyl, C3-10 alkenyl, cycloalkyl, Ph, C5-8 cycloalkenyl, oxadiazolylalkyl, (methyloxodioxolyl)methyl, etc.; n = 0-4), showing good peripheral .mu. **opioid** receptor antagonism, are prepd. These compds. are useful for the prevention of peripheral side effects assocd. with the use of **opioid** analgesics, including constipation, nausea, and vomiting. Trans-(+)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (prepn. given) and H2C:C(EtO2C)CH2Ph in MeOH were stirred at room temp. to give trans-I (R1 = H, R2 = Me, R3 = PhCH2, A = OEt, n = 1) , isolated as the HCl salt. Pharmaceutical formulations comprising I are given.

IT **145603-87-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 145603-87-8 CAPLUS

CN Glycine, N-[(2R)-2-[[(3S,4S)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-, 2-methylpropyl ester (9CI) (CA INDEX NAME)

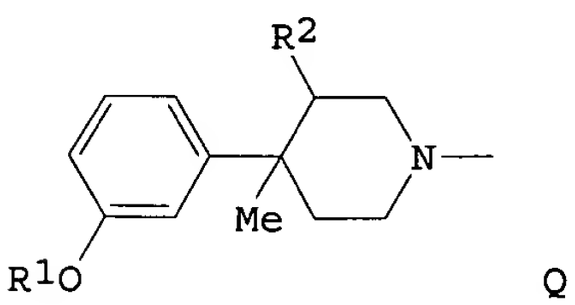
Absolute stereochemistry.



L5 ANSWER 32 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:212896 CAPLUS
DOCUMENT NUMBER: 118:212896
TITLE: Preparation and formulation of N-[(acylamino)alkyl]-4-(3-hydroxyphenyl)piperidines and analogs as peripheral **opioid** antagonists
INVENTOR(S): Cantrell, Buddy Eugene; Zimmerman, Dennis Michael
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA
SOURCE: Eur. Pat. Appl., 77 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 506468	A1	19920930	EP 1992-302729	19920327
EP 506468	B1	19950426		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, PT, SE				
US 5159081	A	19921027	US 1991-677708	19910329
CA 2064382	AA	19920930	CA 1992-2064382	19920327
JP 05097807	A2	19930420	JP 1992-70803	19920327
JP 3059292	B2	20000704		
ES 2072096	T3	19950701	ES 1992-302729	19920327
US 5270328	A	19931214	US 1992-905940	19920629

PRIORITY APPLN. INFO.: US 1991-677708 A 19910329
OTHER SOURCE(S): MARPAT 118:212896
GI



Q

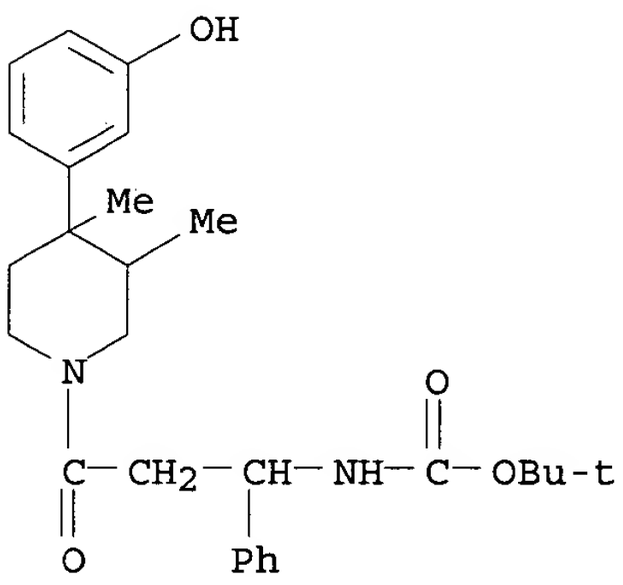
AB R(CH2)nCHR3NR4R5 [I; R = hydroxyphenylpiperidino group Q; R1 = H, alkyl;

R2 = H, alkyl, alkenyl; R3 = H, (cyclo)alkyl, (cyclo)alkenyl, Ph, phenylalkyl, etc.; R4 = (cyclo)alkyl, alkenyl, Ph, phenylalkyl, etc.; R5 = H, alkyl, alkanoyl, alkylcarbamyl, [CO(CH2)mCO]qR6, etc.; n, m, q = 1-3; R6 = OH, alkoxy, NH2, alkylamino, etc.] were prepd. Thus, cyclohexylacetaldehyde was condensed with CH2(CO2H)2 in the presence of NH4OAc and the protected product condensed with trans-QH (R2 = Me, R1 = H) to give, after deprotection and redn., QCH2CH2CHR3NH2 (R3 = cyclohexylmethyl) which was condensed with succinic anhydride to give Q(CH2)mCHR3NHCO(CH2)nCOR6 (R1 = H, R3 = cyclohexylmethyl) (II; R2 = Me, R6 = OH, m = n = 2). II (R2 = Me, R6 = OCH2CHMe2, n = 3, m = 1) had ED50 of 0.002 mg/kg s.c. or orally for pptn. of opiate abstinence in mice.

IT **145340-48-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, in prepn. of peripheral **opioid** antagonists)

RN 145340-48-3 CAPLUS

CN Carbamic acid, [3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-3-oxo-1-phenylpropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 33 OF 49 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1993:183218 CAPLUS

DOCUMENT NUMBER: 118:183218

TITLE: Phenylpiperidine **opioid** antagonists that promote weight loss in rats have high affinity for the .**kappa**.2B (enkephalin-sensitive) binding site

AUTHOR(S): Rothman, Richard B.; Xu, Heng; Char, George U.; Kim, Andrew; De Costa, Brian R.; Rice, Kenner C.; Zimmerman, Dennis M.

CORPORATE SOURCE: Clin. Psychopharmacol. Sect., NIDA, Baltimore, MD, 21224, USA

SOURCE: Peptides (New York, NY, United States) (1993), 14(1), 17-20
CODEN: PPTDD5; ISSN: 0196-9781

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Certain **opioid** antagonists of the phenylpiperidine series (PPAs), such as LY255582, seem uniquely efficacious at producing wt. loss in lean and meal-fed obese Zucker rats. Comparison of the pharmacol. and receptor binding profile of PPAs that promote marked wt. loss with those that do not has failed to find any obvious differences between these two groups of narcotic antagonists, which might explain the differences in their biol. activities. The potent stimulatory effect of dynorphin, and other .**kappa**. agonists, on feeding behavior suggests that the antagonists that promote wt. loss might have high affinity for .

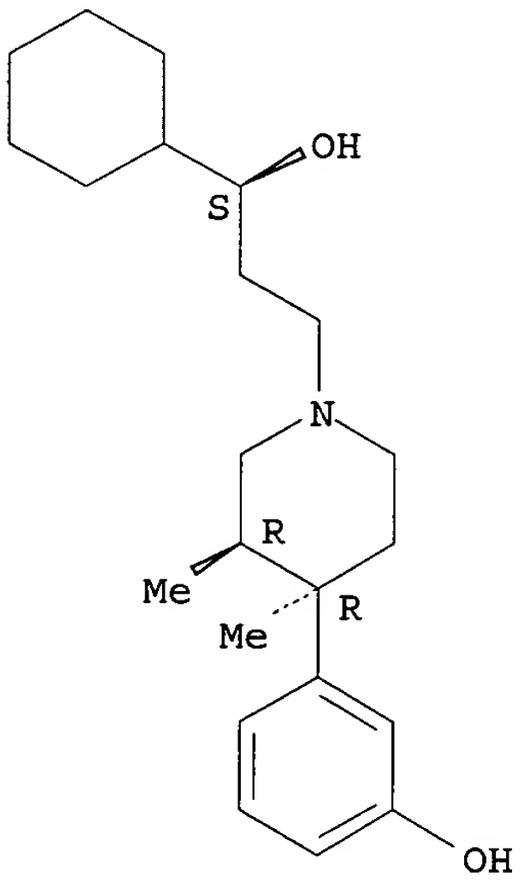
kappa. receptors. The recent demonstration by several labs. of . **kappa**. receptor heterogeneity prompted us to test the hypothesis that the antagonists that promote wt. loss might have high affinity for a subtype of .**kappa**. binding sites. In the present study, therefore, we detd. the Ki values of five PPAs, naloxone, and naltrexone at .mu., .delta., .**kappa**.1, .**kappa**.2a, and . **kappa**.2b binding sites. The data indicate that antagonists having subnanomolar Ki values and high selectivity for the .**kappa**.2b binding site (relative to the .**kappa**.2a binding site) are efficacious at promoting wt. loss.

IT **119193-09-8**, LY255582
RL: BIOL (Biological study)
(binding to **opioid** and .**kappa**.2B receptors, anorectic activity in relation to)

RN 119193-09-8 CAPLUS

CN 1-Piperidinepropanol, .alpha.-cyclohexyl-4-(3-hydroxyphenyl)-3,4-dimethyl-, (.alpha.S,3R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 34 OF 49 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1993:124401 CAPLUS

DOCUMENT NUMBER: 118:124401

TITLE: Preparation of .omega.-(4-phenylpiperidino)alkanoates as peripheral **opioid** receptor receptor antagonists

INVENTOR(S): Cantrell, Buddy Eugene; Zimmerman, Denis Michael

PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA

SOURCE: Eur. Pat. Appl., 79 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

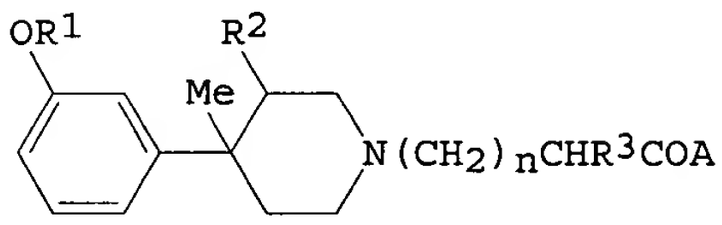
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 506478	A1	19920930	EP 1992-302751	19920327
EP 506478	B1	19970903		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, PT, SE

ZA 9202180	A	19930927	ZA 1992-2180	19920325
CZ 284993	B6	19990414	CZ 1992-902	19920325
NO 9201182	A	19920930	NO 1992-1182	19920326
NO 178398	B	19951211		
NO 178398	C	19960320		
HU 66596	A2	19941228	HU 1992-1013	19920326
IL 101382	A1	19970415	IL 1992-101382	19920326
AU 9213880	A1	19921001	AU 1992-13880	19920327
AU 644051	B2	19931202		
BR 9201084	A	19921124	BR 1992-1084	19920327
JP 05097806	A2	19930420	JP 1992-70790	19920327
JP 3056321	B2	20000626		
RU 2076863	C1	19970410	RU 1992-5011276	19920327
AT 157653	E	19970915	AT 1992-302751	19920327
ES 2106825	T3	19971116	ES 1992-302751	19920327
CN 1065455	A	19921021	CN 1992-102213	19920328
CN 1041309	B	19981223		
US 5250542	A	19931005	US 1992-916783	19920717

PRIORITY APPLN. INFO.: US 1991-677042 A 19910329
OTHER SOURCE(S): MARPAT 118:124401
GI



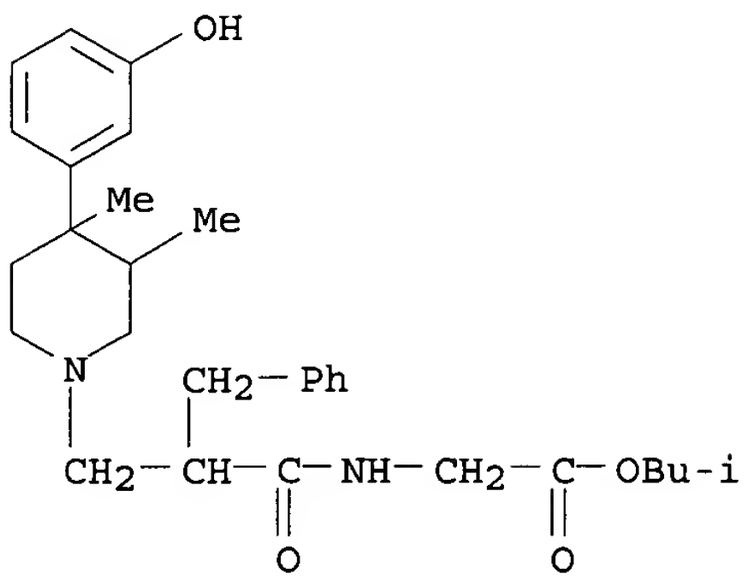
I

AB Title compds. I (R1 = H, C1-5 alkyl; R2 = H, C1-3 alkyl, C2-6 alkenyl; R3 = H, C1-10 alkyl, C1-10 alkenyl, Ph, cycloalkyl, etc.; A = R4O, R6R5N wherein R4 = H, C1-10 alkyl, C2-10 alkenyl, cycloalkyl, etc., R5 = H, C1-3 alkyl, R6 = H, C1-10 alkyl, C3-10 alkenyl, cycloalkyl, Ph, HO2C(CH2)3NH, etc., R5R6 are each CH2 which together with N form 4-6-membered heterocyclyl, etc., n = 0-4) or a part thereof, useful as peripheral **opioid** antagonists, are prepd. I.HCl (R1 = H, R2 = Me, R3 = cyclohexyl, n = 2, A = HO) (prepn. given), H2N(CH2)3CO2Et.HCl and Et3N in DMF were combined with DCC to give I [R1 = H, R2 = Me, R3 = cyclohexyl, n = 2, A = EtO2C(CH2)3NH].HCl which was converted to the free acid (II). II showed the greatest antagonism of the peripheral **opioid** receptors. Pharmaceutical formulations comprising I are given.

IT **145591-02-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and conversion to diastereomers)

RN 145591-02-2 CAPLUS

CN Glycine, N-[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-, 2-methylpropyl ester (9CI) (CA INDEX NAME)



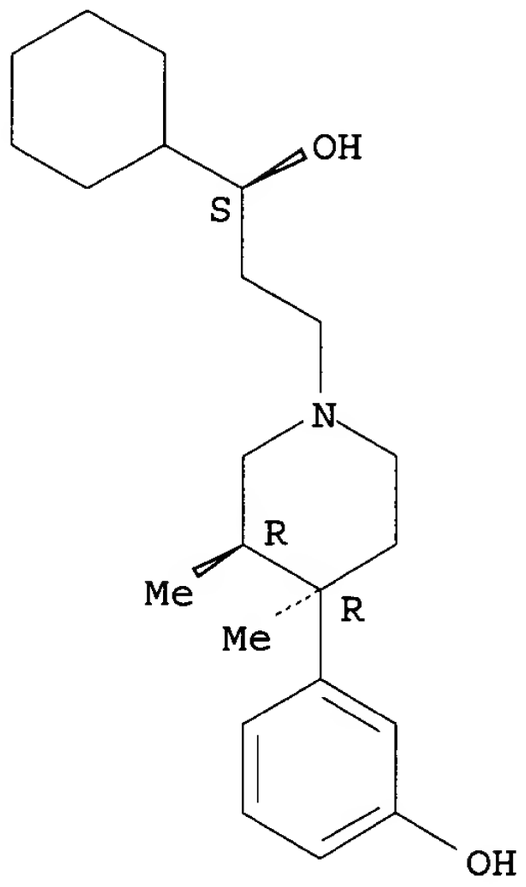
L5 ANSWER 35 OF 49 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1992:99183 CAPLUS
DOCUMENT NUMBER: 116:99183
TITLE: Central administration of the **opioid** antagonist, LY255582, decreases short- and long-term food intake in rats
AUTHOR(S): Levine, A. S.; Grace, M.; Billington, C. J.; Zimmerman, D. M.
CORPORATE SOURCE: Res. Serv., VA Med. Cent., Minneapolis, MN, 55417, USA
SOURCE: Brain Research (1991), 566(1-2), 193-7
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A variety of **opioid** antagonists have been reported to decrease short-term food intake, but few appear to reduce long-term intake. In the present study the authors evaluated the effect of a relatively new class of **opioid** antagonists, 3,4-dimethyl-4-phenylpiperidines, on short-term and long-term food intake after central administration. They also evaluated their affinities for the .mu. and .**kappa**. **opioid** receptor sites in synaptosomal membranes derived from rat whole brain tissue (minus cerebellum) and guinea-pig cortex, resp. The affinities for the .mu. receptor sites were LY255582 > LY217273 > LY256897 > naloxone > LY227444. The affinities for the .**kappa**. receptor sites were LY255582 .vphi. LY256897 = LY217273 > LY227444. LY255582 reduced food intake for up to 24 h after a single intraventricular injection. Doses as low as 1 .mu.g of LY255582 decreased food intake for up to 4 h. All other drugs were much less powerful. Naloxone and LY256897 only decreased food intake after injection of the 100 .mu.g dose. LY227444 and LY217273 failed to decrease intake at all doses tested. LY255582 (100 .mu.g) decreased food intake over a 7 day period when injected intraventricularly once per day. The body wt. of the rats also decreased during the 7 day period. Upon cessation of drug administration body wts. and food intake approached control levels. Thus, LY255582 appears to be a very potent and long-acting anorectic agent which may be useful in the treatment of obesity. The .mu. and .**kappa**. binding profile of the phenylpiperidines does not seem to clearly correlate with their anorectic activity.

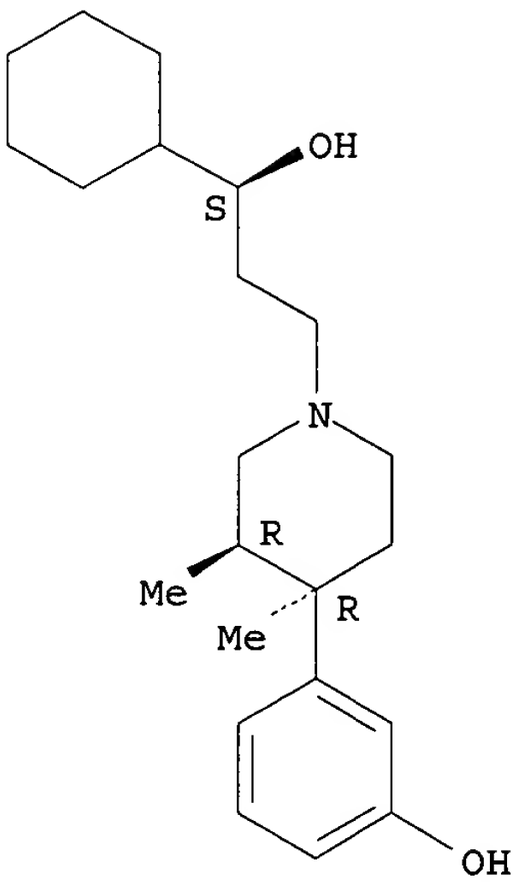
IT **119193-09-8**, LY 255582
RL: BIOL (Biological study)
(food intake inhibition by, **opioid** receptor binding affinity in relation to)
RN 119193-09-8 CAPLUS
CN 1-Piperidinepropanol, .alpha.-cyclohexyl-4-(3-hydroxyphenyl)-3,4-dimethyl-, (.alpha.S,3R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

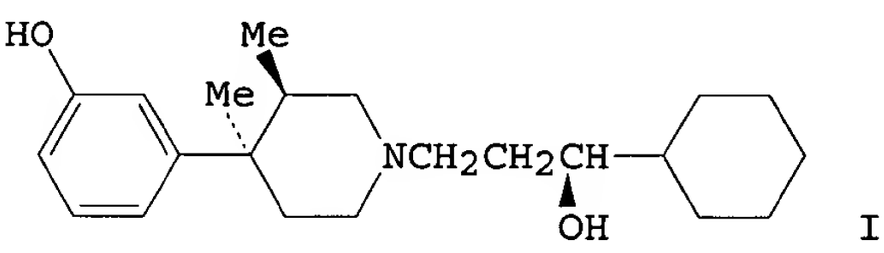


L5 ANSWER 36 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:41202 CAPLUS
DOCUMENT NUMBER: 116:41202
TITLE: Synthesis and absolute configuration of LY255582, a potent **opioid** antagonist
AUTHOR(S): Lessor, Ralph A.; Lenz, George R.; Evans, Suzanne M.
CORPORATE SOURCE: BOC Group Tech. Cent., USA
SOURCE: Chemtracts: Organic Chemistry (1991), 4(5), 396-400
CODEN: CMOCEI; ISSN: 0895-4445
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB The title research of C. H. Mitch, et al. (1991) is reviewed with commentary and 5 refs.
IT **119193-09-8P**, LY 255582
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and abs. configuration of)
RN 119193-09-8 CAPLUS
CN 1-Piperidinepropanol, .alpha.-cyclohexyl-4-(3-hydroxyphenyl)-3,4-dimethyl-, (.alpha.S,3R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 37 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:526783 CAPLUS
DOCUMENT NUMBER: 115:126783
TITLE: The effect of the **opioid** antagonist LY255582 on body weight of the obese Zucker rat
AUTHOR(S): Shaw, Walter N.; Mitch, Charles H.; Leander, J. David; Mendelsohn, Laurane G.; Zimmerman, Dennis M.
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: International Journal of Obesity (1991), 15(6), 387-95
CODEN: IJOBDP; ISSN: 0307-0565
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

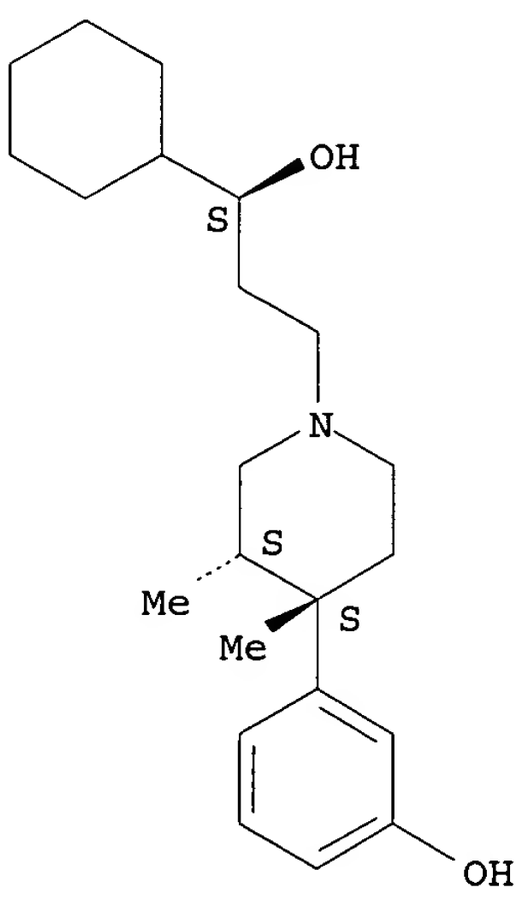
AB The effects of the phenylpiperidine **opioid** antagonist LY255582 (I) on food consumption, water consumption, and body wt. gain of the meal-fed obese Zucker rat were detd. A single s.c. dose of LY255582 (0.31 mg/kg) decreased food and water consumption. LY255582 was effective as an appetite suppressant at lower doses than ephedrine, amphetamine, fenfluramine, naltrexone, and nalmefene. Comparison of the relative in vivo biol. activity with in vitro receptor binding assays of LY255582 and its stereoisomers showed that the order of the affinity of the .mu. and . **kappa**. **opioid** receptors correlated well with the biol. activity. LY255582 was the most biol. effective and had the highest affinity for both receptors. LY255582 administered chronically for 68 days at 0.31 mg/kg reduced food and water consumption and decreased body wt. gains during the entire treatment period. There was no development of tolerance to the biol. effects of LY255582.

IT **119193-08-7**, LY 255609

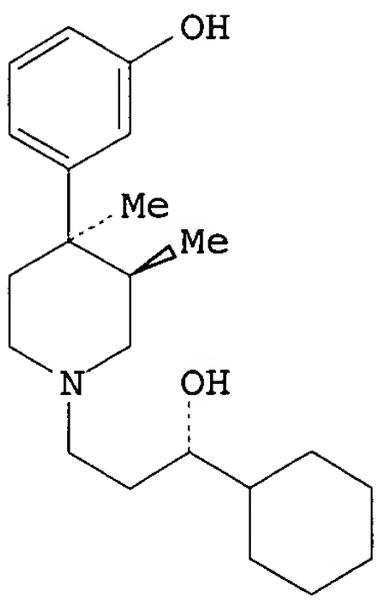
09/ 755,021

RL: BIOL (Biological study)
(feeding and body wt. in obesity response to, **opioid** receptors in relation to)
RN 119193-08-7 CAPLUS
CN 1-Piperidinepropanol, .alpha.-cyclohexyl-4-(3-hydroxyphenyl)-3,4-dimethyl-, (.alpha.S,3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 38 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:163942 CAPLUS
DOCUMENT NUMBER: 114:163942
TITLE: Synthesis and absolute configuration of LY255582, a potent **opioid** antagonist
AUTHOR(S): Mitch, Charles H.; Zimmerman, Dennis M.; Snoddy, John D.; Reel, Jon K.; Cantrell, Buddy E.
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Journal of Organic Chemistry (1991), 56(4), 1660-3
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 114:163942
GI



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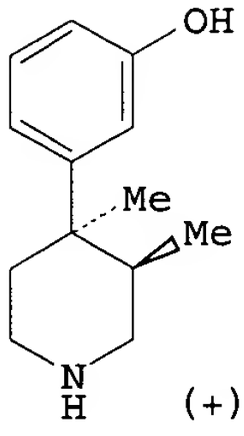
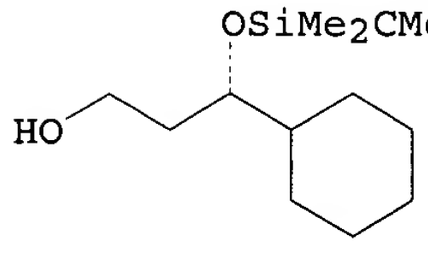


(+)-II



(-)-III

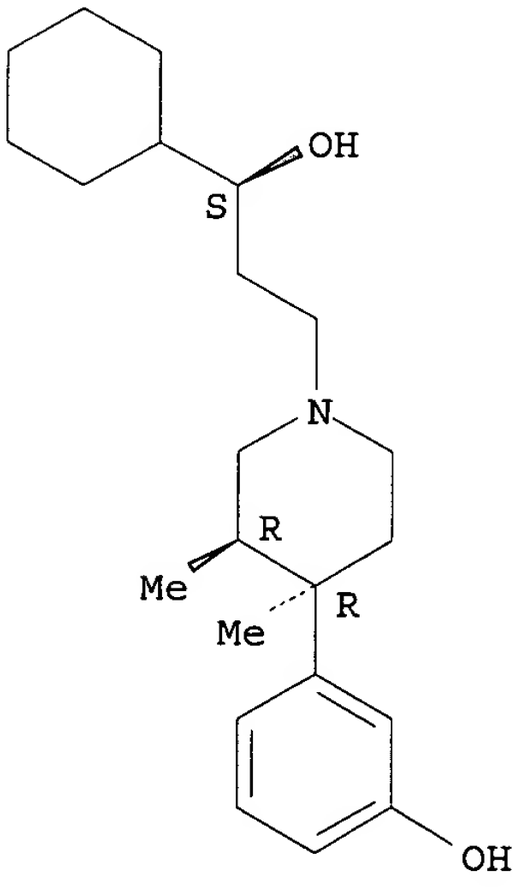
AB LY255582, (+)-I, was prepd. by a convergent route based on the coupling of optically pure arylpiperidine and cyclohexylpropanol subunits. The 3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine unit, (+)-II, was derived from 1-methyl-4-(3-methoxyphenyl)-1,2,5,6-tetrahydropyridine by metalation and alkylation with MeI followed by a Mannich reaction between the resulting enamine, formaldehyde and dimethylamine. Stereoselective redn., resoln. with dibenzoyl tartaric acid and cleavage of the N-Me and O-Me groups with vinyl chloroformate and HBr/acetic acid, resp., afforded subunit (+)-II. Sharpless kinetic resoln. of 1-hydroxy-1-cyclohexyl-2-propene, followed by protection with tert-BuMe2SiCl and hydroboration gave the silyl protected 1,3-dihydroxy-1-cyclohexylpropane (-)-III. Primary mesylation of (-)-III and coupling with the arylpiperidine (+)-II, gave LY255582. The abs. configuration of LY255582 was established from the kinetic resoln. process along with x-ray crystallog. detn. of relative stereochem.

IT **119193-09-8P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and abs. configuration of)

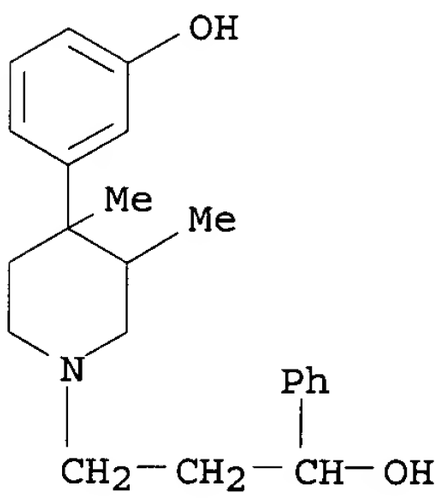
RN 119193-09-8 CAPLUS

CN 1-Piperidinepropanol, .alpha.-cyclohexyl-4-(3-hydroxyphenyl)-3,4-dimethyl-, (.alpha.S,3R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 39 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:452340 CAPLUS
DOCUMENT NUMBER: 113:52340
TITLE: Effect of phenylpiperidine **opioid** antagonists on food consumption and weight gain of the obese Zucker rat
AUTHOR(S): Shaw, Walter N.; Mitch, Charles H.; Leander, J. David; Zimmerman, Dennis M.
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1990), 253(1), 85-9
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Meal-fed Zucker rats were used to det. the acute and chronic s.c. effect of 4 trans-3,4-dimethyl-4-phenylpiperidines (**opioid** antagonists) on food consumption. In acute studies, the active compds. suppressed food intake by lean and obese meal-fed Zucker rats. LY117413 was the most effective over the 4-h period immediately after its s.c. administration. Long-term chronic s.c. administration to the meal-fed obese Zucker rat showed that LY88329 and LY117413 reduced food consumption for as long as the drug was administered, causing a decrease in body wt. gain when compared to nontreated control obese rats. There was no evidence for the development of tolerance to these effects of LY88329 and LY117413 in this genetically obese rat model.
IT **82970-70-5**, LY 117413
RL: BIOL (Biological study)
(feeding and wt. gain in obesity response to, narcotic antagonism in relation to)
RN 82970-70-5 CAPLUS
CN 1-Piperidinepropanol, 4-(3-hydroxyphenyl)-3,4-dimethyl-.alpha.-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 40 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:95017 CAPLUS
DOCUMENT NUMBER: 110:95017
TITLE: Preparation of 4-phenylpiperidines as **opioid** antagonists
INVENTOR(S): Mitch, Charles Howard; Zimmerman, Dennis Michael
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA
SOURCE: Eur. Pat. Appl., 44 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 287339	A2	19881019	EP 1988-303302	19880413
EP 287339	A3	19910515		
EP 287339	B1	19940817		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
IL 86061	A1	19920715	IL 1988-86061	19880413
CA 1321792	A1	19930831	CA 1988-563995	19880413
ES 2058265	T3	19941101	ES 1988-303302	19880413
AU 8814624	A1	19881020	AU 1988-14624	19880414
AU 596290	B2	19900426		
DK 8802043	A	19890105	DK 1988-2043	19880414
ZA 8802640	A	19891227	ZA 1988-2640	19880414
SU 1598869	A3	19901007	SU 1988-4355530	19880414
CN 88102191	A	19881102	CN 1988-102191	19880415
CN 1017992	B	19920826		
JP 63277661	A2	19881115	JP 1988-94395	19880415
HU 46892	A2	19881228	HU 1988-1968	19880415
HU 202492	B	19910328		
US 4891379	A	19900102	US 1988-284504	19881214
US 4992450	A	19910212	US 1989-448800	19891211
US 5064834	A	19911112	US 1990-605817	19901030
US 5319087	A	19940607	US 1992-939794	19920903
US 5422356	A	19950606	US 1994-252496	19940601

PRIORITY APPLN. INFO.:

US 1987-39121	19870416
US 1988-284504	19881214
US 1989-448800	19891211
US 1990-605817	19901030
US 1991-747317	19910820
US 1992-939794	19920903

OTHER SOURCE(S): MARPAT 110:95017

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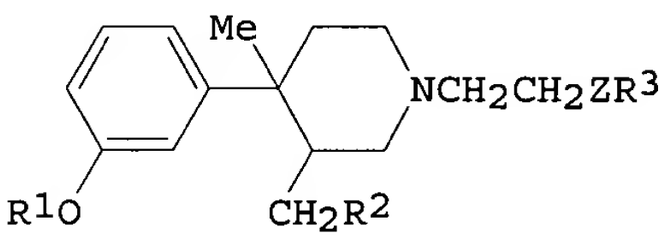

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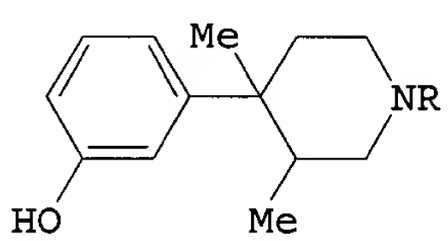


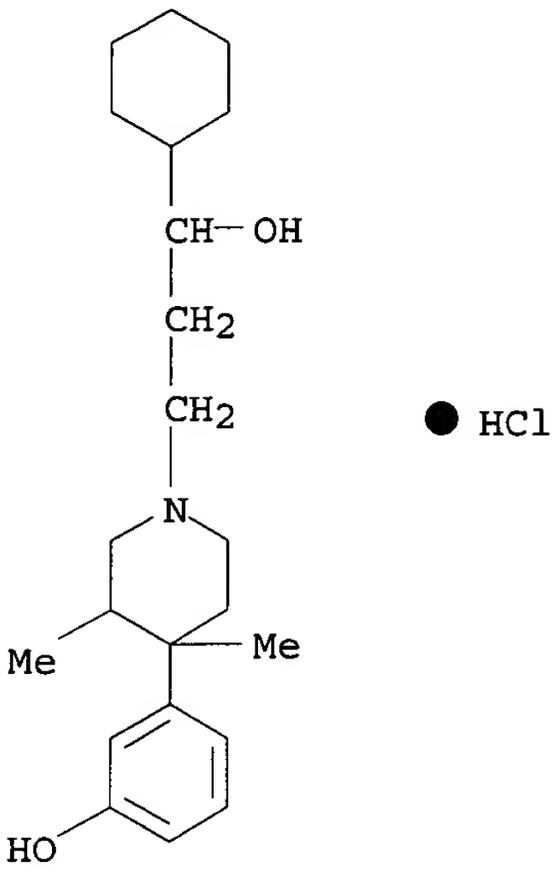
II

AB The title compds. [I; R1 = H, alkanoyl; R2 = H, alkyl, alkenyl; R3 = cycloalkyl, cycloalkenyl, alkyl, alkenyl, thienyl; Z = bond, CO, CHOR4; R4 = H, alkyl, (CH2)nPh, COR5; R5 = alkyl, (CH2)nPh; n = 1-3] were prepd. trans-(+)-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidine was refluxed 2 h with BuCH2COCl in DMF contg. Et3N and the product stirred .apprx.1 h with (MeOCH2CH2O)2AlH2Na in PhMe to give title compd. trans-(+)-II (R = hexyl) which gave 50% inhibition of mu and **kappa** receptor-mediated analgesia in mice at 0.26 and 0.22 mg/kg s.c., resp. Capsules were prepd. each contg. trans-(+)-II.HCl (R = S-3-hydroxy-3-cyclohexylpropyl) 250, starch 200, and Mg stearate 10 mg.

IT **119192-92-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as **opioid** antagonist)

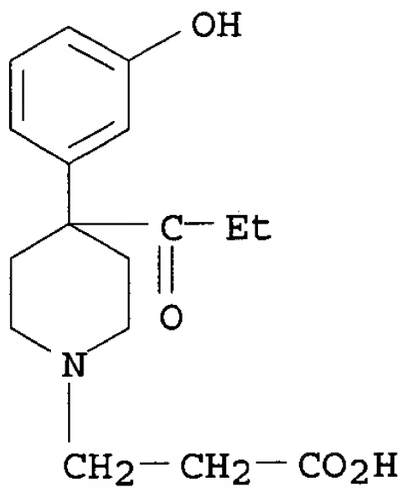
RN 119192-92-6 CAPLUS

CN 1-Piperidinepropanol, .alpha.-cyclohexyl-4-(3-hydroxyphenyl)-3,4-dimethyl-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

L5 ANSWER 41 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:649 CAPLUS
DOCUMENT NUMBER: 110:649
TITLE: Evaluation of new compounds for **opioid** activity: 1987 annual report
AUTHOR(S): Woods, James; Medzihradsky, Fedor; Smith, Charles; Winger, Gail; Gmerek, Debra
CORPORATE SOURCE: Dep. Pharmacol., Univ. Michigan, Ann Arbor, MI, 48109, USA
SOURCE: NIDA Research Monograph (1988), 81(Probl. Drug Depend., 1987), 543-90
CODEN: MIDAD4; ISSN: 0361-8595
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB In vivo and in vitro studies on compds. known for opiate activity and **opioid** activity of new compds. are described.
IT **117332-78-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**opioid** activity of, evaluation of)
RN 117332-78-2 CAPLUS
CN 1-Piperidinepropanoic acid, 4-(3-hydroxyphenyl)-4-(1-oxopropyl)-, hydrochloride (9CI) (CA INDEX NAME)

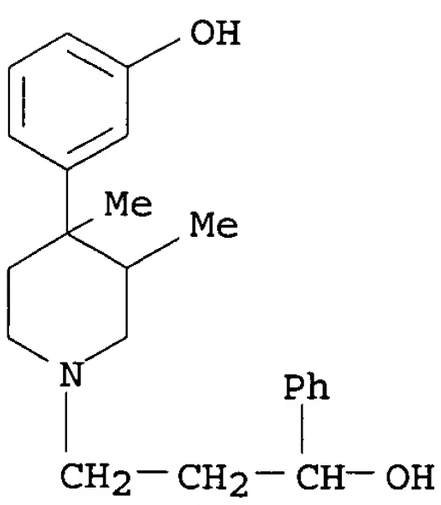


⊙ HCl

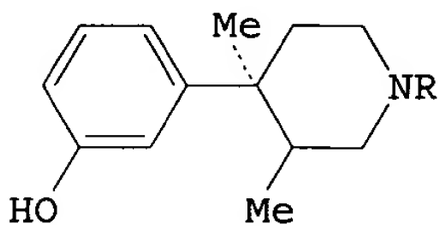
L5 ANSWER 42 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1988:402295 CAPLUS
DOCUMENT NUMBER: 109:2295
TITLE: Further studies of opioids and intake of sweetened alcoholic beverage
AUTHOR(S): Hubbell, Christopher L.; Abelson, Michael L.; Wild, Kenneth D.; Neuman, Regina; Reid, Larry D.
CORPORATE SOURCE: Dep. Psychol., Rensselaer Polytech. Inst., Troy, NY, 12180-3590, USA
SOURCE: Alcohol (New York, NY, United States) (1988), 5(2), 141-6
CODEN: ALCOEX; ISSN: 0741-8329
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rats were placed on a daily regimen of water deprivation followed by a limited opportunity to take either water or a sweetened alc. beverage. Across days of opportunity, they took less water and more alc. until they were taking considerable amts. of alc. Naloxone, given prior to opportunity to drink, reduced intakes of alc. beverage. Small doses of morphine increased intakes of alc. beverage at doses as low as 0.41 mg/kg. Two other antagonists at **opioid** receptors (LY 117413 and MR2266) also reduced alc. intake. Apparently endogenous **opioid** systems are involved in modulating intake of alc.

IT **82970-70-5**, LY 117413
RL: BIOL (Biological study)
(ethanol consumption inhibition by, **opioid** receptors in relation to)
RN 82970-70-5 CAPLUS
CN 1-Piperidinepropanol, 4-(3-hydroxyphenyl)-3,4-dimethyl-.alpha.-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 43 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:563223 CAPLUS
DOCUMENT NUMBER: 101:163223
TITLE: Antagonism of bremazocine-induced urination as a test for **kappa-opioid** receptor antagonists within the phenylpiperidine series
AUTHOR(S): Leander, J. David; Zimmerman, Dennis M.
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Drug Development Research (1984), 4(4), 421-7
CODEN: DDREDK; ISSN: 0272-4391
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

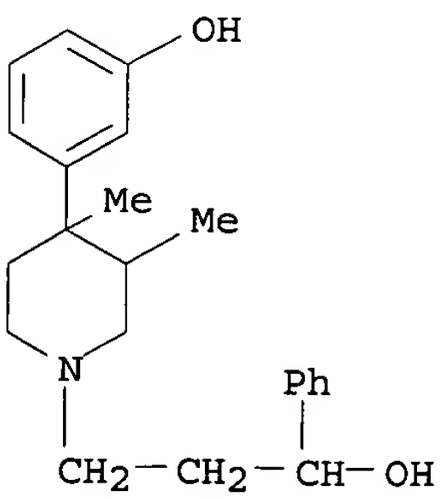


I

AB Several phenylpiperidines (I, R Me, phenylalkyl, or allyl) were compared in their ability to antagonize the diuretic effect of 0.08 mg/kg of bremazocine [75684-07-0], a .**kappa**.-**opioid** receptor agonist. Three of the compds. {LY 106737 I (R = CH2CH2Ph) [82970-72-7], LY 117413 I [R = CH2Ch2CH(OH)Ph] [**82970-70-5**], and LY 88329 I (R = CH2CH2COPh) [78693-86-4]} produced dose-related antagonism of bremazocine, whereas 4 others did not. The 4 ineffective I also did not exhibit any .**kappa**. agonist activity. The potency of the 3 effective I did not correlate with their antagonist activity against morphine or in suppressing deprivation-induced drinking. Apparently, several .**kappa**.-receptor antagonists can be found in the I series of **opioid** antagonists. This emphasizes the usefulness of .**kappa**.-mediated diuresis as an in vivo test for .**kappa**.-**opioid** receptor activity.

IT **82970-70-5**
RL: BIOL (Biological study)
(bremazocine diuresis antagonism by, .**kappa**.-receptor activity in relation to)

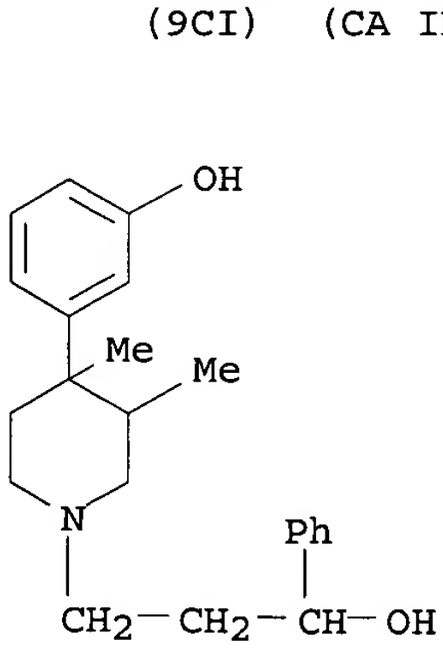
RN 82970-70-5 CAPLUS
CN 1-Piperidinepropanol, 4-(3-hydroxyphenyl)-3,4-dimethyl-.alpha.-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 44 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:61632 CAPLUS
DOCUMENT NUMBER: 100:61632
TITLE: Further study of **kappa** opioids on increased urination
AUTHOR(S): Leander, J. David
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1983), 227(1), 35-41
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of various **opioid** agonists and antagonists on urination were studied in the normally hydrated rat. Two .**kappa**. agonists, U-50488H [83913-06-8] and proxorphan tartrate [69815-39-0], markedly increased urination. The increased urination produced by U-50,488H was antagonized by **opioid** antagonists in a potency order which indicated that the effects were due to an action at .**kappa**. **opioid** receptors. .mu. Agonists decreased urination and were blocked by low doses (0.01 and 0.1 mg/kg) of naloxone [465-65-6], whereas .**kappa**. agonists increased urination and were only blocked by a high dose (10 mg/kg) of naloxone. The diuretic effects of U-50,488H and ketazocine [36292-69-0], but not proxorphan and bremazocine [75684-07-0], were reduced by morphine [57-27-2], consistent with the idea that proxorphan and bremazocine have morphine antagonist activity. Water derivation produced a shift to the right for the dose-effect curve for bremazocine-induced diuresis. .**kappa**. Agonists were ineffective in increasing urination in Brattleboro rats that were homozygous for diabetes insipidus, whereas .mu. agonists were still effective in decreasing urination. Apparently, .**kappa**. agonists inhibit release of vasopressin [11000-17-2] from the neurohypophysis and this decrease in vasopressin release leads to increased urination. The effects of opioids on urination in the normally hydrated rat can be extremely useful in classifying the activities of **opioid** on .mu. and .**kappa**. receptors in vivo.

IT **82970-70-5**
RL: BIOL (Biological study)
(narcotic antagonist potency of, against diuresis from .**kappa**. -opiates)
RN 82970-70-5 CAPLUS
CN 1-Piperidinepropanol, 4-(3-hydroxyphenyl)-3,4-dimethyl-.alpha.-phenyl- (9CI) (CA INDEX NAME)



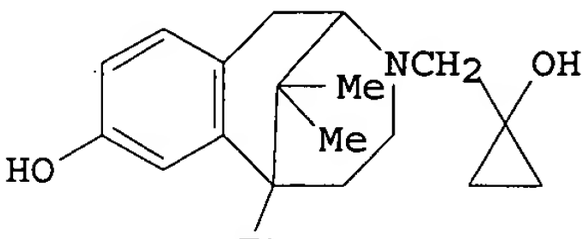
L5 ANSWER 45 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:119519 CAPLUS
DOCUMENT NUMBER: 98:119519
TITLE: A **kappa opioid** effect: increased

urination in the rat

AUTHOR(S): Leander, J. David
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1983), 224(1), 89-94
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

GI

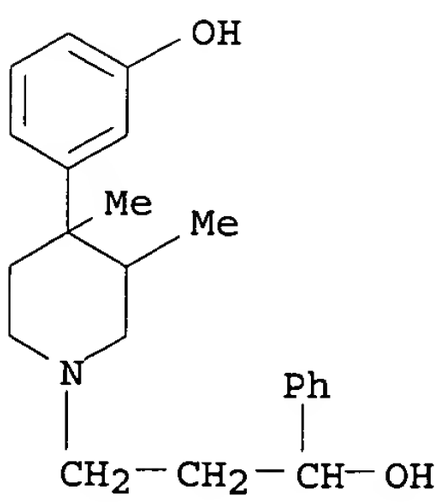


Et I

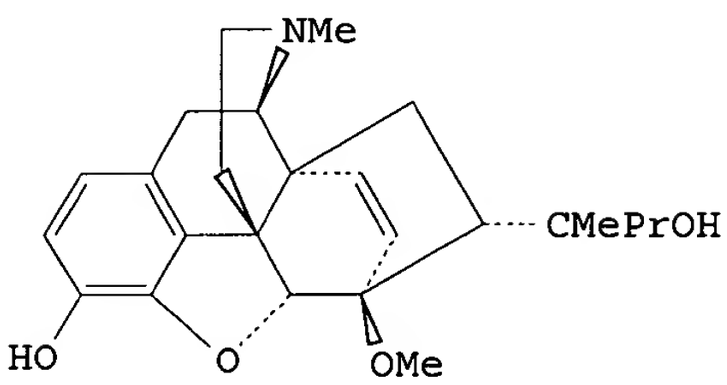
AB The effects of various opioids (.mu. agonists, .**kappa**. agonists and mixed agonists/antagonists) were detd. on urination in the normally hydrated rat. Opioids considered as .**kappa**. agonists bremazocine (I) [75684-07-0], ethylketazocine methane sulfonate [60183-11-1], and ketazocine [36292-69-0] produced a marked dose-related increase in urination. The mixed agonists/antagonists (cyclazocine [3572-80-3], butorphanol tartrate [58786-99-5], and nalorphine [62-67-9]) produced less urination than the .**kappa**. agonists, but more than the .mu. agonists (morphine [57-27-2] and l-methadone [125-58-6]). The .mu. agonists did not increase urine output compared with controls. The increased urination effect was blocked by **opioid** antagonists in a potency order which indicated that the effect was due to an action at a .**kappa**. **opioid** receptor. Apparently, dynorphin [74913-18-1], a .**kappa**. agonist acts as an endogenous ligand for an autoreceptor which inhibits the corelease of dynorphin and antidiuretic hormone [11000-17-2] from the neurohypophysis. This decrease in antidiuretic hormone levels produces the increased urination. Increased urination is a simple in vivo test for studying the actions of compds. at .**kappa**. **opioid** receptors.

IT **82970-70-5**
RL: BIOL (Biological study)
(diuretic activity of opiates in relation to)

RN 82970-70-5 CAPLUS
CN 1-Piperidinepropanol, 4-(3-hydroxyphenyl)-3,4-dimethyl-.alpha.-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 46 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:592666 CAPLUS
DOCUMENT NUMBER: 97:192666
TITLE: Potencies of "mu" and "**kappa**" agonists on smooth muscle preparations relative to displacement of 3H-etorphine in isolated rat brain neural membranes
AUTHOR(S): Smith, C. B.; Medzihradsky, F.
CORPORATE SOURCE: Med. Sch., Univ. Michigan, Ann Arbor, MI, 48109, USA
SOURCE: Adv. Endog. Exog. Opioids, Proc. Int. Narc. Res. Conf., 12th (1981), 42-4. Editor(s): Takagi, Hiroshi; Simon, Eric J. Kodansha: Tokyo, Japan.
CODEN: 48NVAY
DOCUMENT TYPE: Conference
LANGUAGE: English
GI



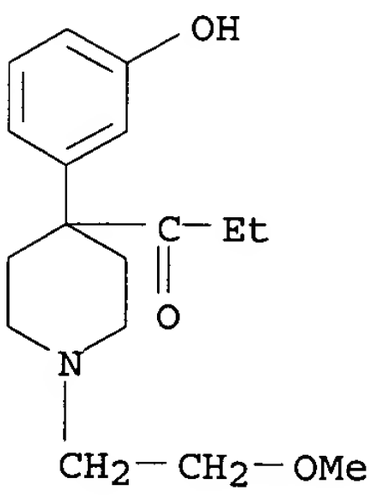
I

AB Tritium-labeled etorphine (I) [57-27-2] binds to sites in isolated rat brain neural membranes which most closely resemble the opiate receptors stimulated by .mu.-agonist in the mouse vas deferens than in guinea pig ileum. The extreme potency of some opiates upon guinea pig ileum is not matched by a similar potency in displacing I-3H in isolated rat brain neural membranes.

IT **80251-36-1**
RL: BIOL (Biological study)
(binding of, by brain and smooth muscles)
RN 80251-36-1 CAPLUS
CN 1-Propanone, 1-[4-(3-hydroxyphenyl)-1-(2-methoxyethyl)-4-piperidinyl]-, ethanedioate (2:1) (salt) (9CI) (CA INDEX NAME)

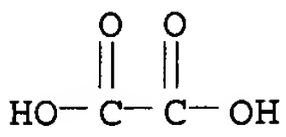
CM 1

CRN 80251-35-0
CMF C17 H25 N O3

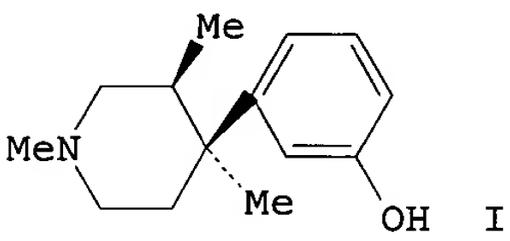


CM 2

CRN 144-62-7
CMF C2 H2 O4



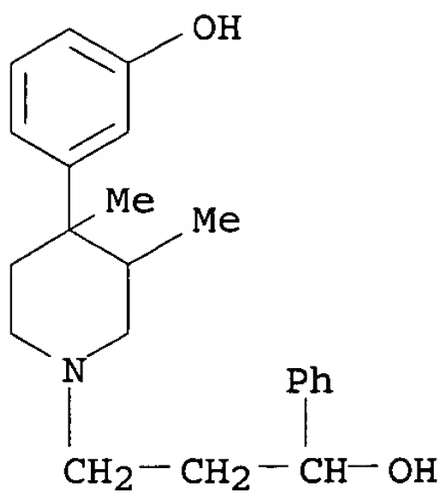
L5 ANSWER 47 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:520129 CAPLUS
DOCUMENT NUMBER: 97:120129
TITLE: Novel phenylpiperidine **opioid** antagonists and partial agonists: effects on fluid consumption
AUTHOR(S): Leander, J. David; Hart, John C.; Lochner, Mary Ann; Hynes, Martin D., III; Zimmerman, Dennis M.
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: European Journal of Pharmacology (1982), 81(2), 185-92
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The effects of 5 **opioid** antagonists, for example LY 99335 (I) [78738-97-3], a racemate partial agonist and its agonist and antagonist optical isomers were studied on deprivation-induced drinking. All compds. had a phenylpiperidine nucleus. The antagonists produced dose-related decreases in drinking, and the potencies for decreasing drinking correlated with morphine-antagonist doses. The racemic partial agonist and its agonist isomer decreased drinking at doses higher than those which produced marked analgesia. Within the class of phenylpiperidine drugs studied, some had less specificity than naloxone for the .mu.-receptor as compared to the .delta.-receptor, but the suppression of drinking was not related to changes in .mu.-to-.delta. ratios.

IT **82970-70-5**
RL: BIOL (Biological study)
(drinking behavior response to, opiate receptors in relation to)
RN 82970-70-5 CAPLUS
CN 1-Piperidinepropanol, 4-(3-hydroxyphenyl)-3,4-dimethyl-.alpha.-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 48 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:28480 CAPLUS
DOCUMENT NUMBER: 96:28480
TITLE: Correlations among certain behavioral, physiological, and biochemical effects of narcotic agonists
AUTHOR(S): Woods, James H.; Katz, Jonathan L.; Young, Alice M.; Medzihradsky, Fedor; Smith, Charles B.
CORPORATE SOURCE: Med. Sch., Univ. Michigan, Ann Arbor, MI, 48109, USA
SOURCE: NIDA Research Monograph (1980), 34, 43-57
CODEN: MIDAD4; ISSN: 0361-8595
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The relative potencies of .**kappa**.-agonists (ethylketazocine-like drugs such as UM 1070 [57203-00-6], UM 909 [72074-75-0] or ketazocine methane sulfonate [71697-06-8]) and .mu.-agonists (morphine-like drugs such as fentanyl citrate [990-73-8], etorphine-HCl [13764-49-3], or UM 1176 [72074-73-8]) in inhibiting the elec.-induced twitch in isolated mouse vas deferens and guinea-pig ileum were compared and correlated to their relative potencies in displacing bound 3H-labeled etorphine from rat cerebrum membrane prepn. or to their potencies in pptg. or suppressing abstinence in morphine-dependent rhesus monkeys. Differences in the relative potencies of .**kappa**.- and .mu.-agonists on the ileum and vas deferens prepns. failed to distinguish the relative agonists types. However, correlations of the effects of either type of agonist in these prepns. with displacement of bound 3H-labeled etorphine did distinguish between .mu.- and .**kappa**.-agonists. Correlations among effects in the vas deferens or ileum with effects in the 14-h withdrawn morphine-dependent monkey displayed differentiations between smooth muscle prepns. but not agonist types; slopes of regression lines of in vivo effects in the ileum were steeper than with effects in the vas deferens, indicating that the effects in the ileum overestimate while effects in the vas deferens underestimate the in vivo potencies of these agonists. In another correlation study, Meperidine-HCl [50-13-5] and its analog, UM 1170 [74716-70-4], suppressed abstinence in the morphine-withdrawn monkey but failed to displace etorphine from isolated brain prepn., indicating that the narcotic action of these 2 compds. was mediated by distinctive recognition sites.

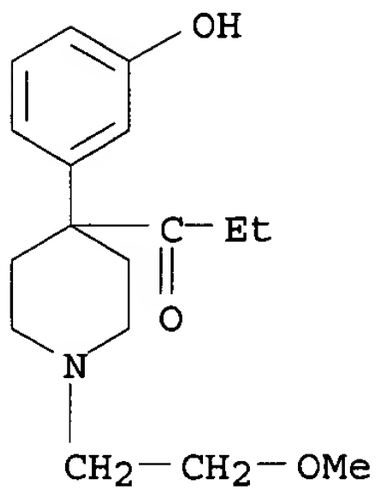
IT **80251-36-1**
RL: PRP (Properties)
(behavioral and biochem. and physiol. effects of, correlation studies of)

RN 80251-36-1 CAPLUS
CN 1-Propanone, 1-[4-(3-hydroxyphenyl)-1-(2-methoxyethyl)-4-piperidinyl]-, ethanedioate (2:1) (salt) (9CI) (CA INDEX NAME)

CM 1

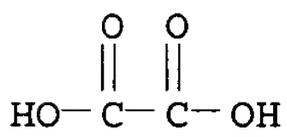
09/ 755,021

CRN 80251-35-0
CMF C17 H25 N O3

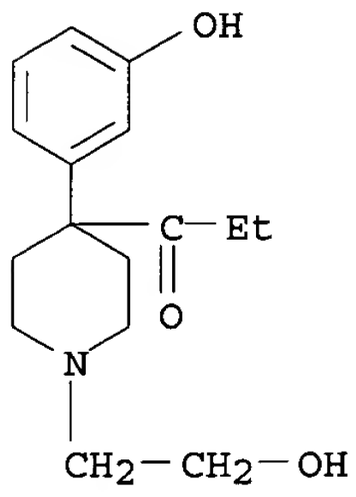


CM 2

CRN 144-62-7
CMF C2 H2 O4



L5 ANSWER 49 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1980:507010 CAPLUS
DOCUMENT NUMBER: 93:107010
TITLE: Annual report: evaluation of new compounds for **opioid** activity (1979)
AUTHOR(S): Swain, Henry H.; Woods, James H.; Medzihradsky, Fedor; Smith, Charles B.; Fly, Clifton L.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Michigan, Ann Arbor, MI, 48109, USA
SOURCE: NIDA Research Monograph (1979), 27(Probl. Drug Depend.), 356-98
CODEN: MIDAD4; ISSN: 0361-8595
DOCUMENT TYPE: Journal
LANGUAGE: English
AB By several evaluation techniques such as phys. dependence evaluation, self-administration (in monkeys), displacement of stereospecific 3H-etorphine binding, depression of twitch in elec. driven guinea pig ileum, and mouse vas deferens prepns., 47 compds. were evaluated for **opioid** activity.
IT **74716-72-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**opioid** activity of)
RN 74716-72-6 CAPLUS
CN 1-Propanone, 1-[1-(2-hydroxyethyl)-4-(3-hydroxyphenyl)-4-piperidinyl]-, hydrobromide (9CI) (CA INDEX NAME)



HBr

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L1             STRUCTURE UPLOADED
L2          1309 S L1 FUL

     FILE 'CAPLUS' ENTERED AT 17:26:40 ON 09 FEB 2003
L3           173 S L2

     FILE 'CAPLUS' ENTERED AT 17:28:51 ON 09 FEB 2003
L4           173 S L3
L5            49 S L4 AND (KAPPA OR OPIOID)

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FULL ESTIMATED COST                                   226.96     376.99

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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